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FOR

INHIBITORS OF FACTOR Xa

INHIBITORS OF FACTOR Xa

Cross Reference to Related Applications

This application claims benefit of priority under 35 U.S.C. § 120 to U.S. Patent Application Serial No. 09/662,807, which claims benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/154,332 filed on September 17, 1999, which are both herein incorporated in their entirety by reference.

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel non-amidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., Thromb. Res. 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly

specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, "Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal $C(=NH)-NH_2$ group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naphthyl group via a straight or branched chain alkylene,-C(=O) or $-S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group

connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds are needed which selectively or preferentially bind to Factor Xa. Compounds with a higher affinity for binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability or other pharmacologically desirable properties.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention provides compounds comprising a five-membered heterocyclic ring structure having from 1-4 hetero atoms selected from the group consisting of N, O and S or a bicyclic ring system comprising the 5-membered heterocyclic ring structure wherein the bicyclic ring structure may have 1-5 hetero atoms selected from the group consisting of N, O and S, and wherein the overall compound has an essentially neutral pH. The compounds according to the invention are potent and selective inhibitors of factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents. Particular embodiments of the compounds of the present invention are set forth below as preferred embodiments and include all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure " and " C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In

each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, aminoloweralkyl, hydroxyloweralkyl, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and

having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary., secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine,

ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

The invention provides a compound of the formula (I):

A-Q-D-E-G-J-X

wherein:

A is selected from:

-$C_{1\text{-}6}$alkyl;

-$C_{3\text{-}8}$cycloalkyl;

phenyl, which is substituted with 0-2 R^1 groups;

naphthyl, which is substituted with 0-2 R^1 groups; and

a 3-10 membered aromatic or non-aromatic heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and is substituted with 0-2 R^1 groups;

R^1 is selected from:

Halo, -CN, -C(=O)-N(R^2, R^3), -NO_2, -SO_2N(R^2, R^3), -SO_2R^2, -$(CH_2)_mNR^2R^3$, -$(CH_2)_m$-C(=NR^3)-R^2, -$(CH_2)_m$-C(=NR^2)-N(R^2,R^3), -$(CH_2)_m$-N(R^2)-C(=NR^2)-N(R^2,R^3), -$(CH_2)_mNR^2$-$C_{3\text{-}6}$heterocyclics, $C_{1\text{-}4}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}8}$cycloalkyl, $C_{0\text{-}4}$alkyl$C_{3\text{-}8}$cycloalkyl, -CF_3, -OR^2, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $C_{1\text{-}4}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}8}$cycloalkyl, $C_{0\text{-}4}$alkyl$C_{3\text{-}8}$cycloalkyl and -NO_2;

R^2 and R^3 are independently selected from the group consisting of:

-H, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, $-CF_3$ and $-NO_2$;

or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

m is an integer of 0-2;

Q is selected from the group consisting of:

a direct link, divalent $-C_1$-$_4$alkyl, divalent $-C_2$-$_4$alkenyl, divalent $-C_{2-4}$alkynyl, -C(=O)-, -C(=NH)-, -C(=NMe)-, $-N(-R^4)-$, $-N(-R^4)-CH_2-$, $-C(=O)-N(-R^4)-$, $-N(-R^4)-C(=O)-$, $-S(=O)_2-$, -O-, $-S(=O)_2-N(-R^4)-$ and $-N(-R^4)-S(=O)_2-$, wherein one or more hydrogens on each of the divalent C_1-$_4$alkyl, divalent C_2-$_4$alkenyl and divalent C_{2-4}alkynyl moieties can be replaced with a $-R^4$ group;

R^4 is selected from the group consisting of:

-H, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, $-CF_3$ and $-NO_2$;

D is selected from the group consisting of:

a direct link;

phenyl, which is substituted with 0-2 R^{1a} groups; and

a 5-10 membered aromatic or non-aromatic heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and the ring system is substituted with 0-2 R^{1a} groups;

R^{1a} is selected from the group consisting of:

halo, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, $-NO_2$, $-(CH_2)_n-N(-R^{2a}, -R^{3a})$, $-S(=O)_2-N(-R^{2a}, -R^{3a})$, $-S(=O)_2-R^{2a}$, $-CF_3$, $-(CH_2)_n-OR^{2a}$, $-C(=O)-O-R^{2a}$, $-C(=O)-N(-R^{2a}, -R^{3a})$, $-C(=NH)-N(-R^{2a}, -R^{3a})$, $-C(=NMe)-N(-R^{2a}, -R^{3a})$, 2-imidazolin-2-yl, 1-methyl-2-imidazolin-2-yl and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the aromatic heterocyclic ring and the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN, $-CF_3$ and $-NO_2$;

R^{2a} and R^{3a} are independently selected from the group consisting of:

-H, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, $-CF_3$ and $-NO_2$;

n is an integer of 0-2;

E is selected from the group consisting of:

a direct link, $-(CH_2)_q-C(=O)-$, $-(CH_2)_q-N(-R^5)-C(=O)-(CH_2)_x-$, $-(CH_2)_q-C(=O)-N(-R^5)-(CH_2)_x-$, $-(CH_2)_q-N(-R^5)-(CH_2)_x-$, , $-(CH_2)_q-N(R^5)CO-NR^6(CH_2)_x$ and $-SO_2-$;

q and x are independently an integer of 0-2;

R^5 and R^6 are independently selected from the group consisting of:

-H, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl, $-C_{1-4}$alkyl-C(=O)-OH, $-C_{0-6}$alkyl-(carbocyclic aryl), $-C_{0-4}$alkyl-(monocyclic heteroaryl) and $-C_{1-4}$alkyl-C(=O)-O-C_{1-4}alkyl, wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety and the monocyclic heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, $-CF_3$ and $-NO_2$;

G is selected from the group consisting of:

phenyl, which is substituted with 0-2 R^{1b} groups; and

a 5-6 membered aromatic heterocyclic ring containing 1-4 hetero atoms selected from N, O and S wherein the heterocyclic ring is substituted with 0-2 R^{1b} groups;

R^{1b} is independently selected from the group consisting of:

halo, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl, $-C_{1-4}$alkyl-C(=O)-OH, -CN, $-NO_2$, $-S(=O)_2-OH$, $-N(-R^{2b}, -R^{3b})$, $-C(=O)-N(-R^{2b}, -R^{3b})$, $-S(=O)_2-N(-R^{2b}, -R^{3b})$,$-S(=O)_2-R^{2b}$, $-CF_3$, $-O-R^{2b}$, $-O-CH_2-CH_2-O-R^{2b}$, $-O-CH_2-C(=O)-O-R^{2b}$, $-N(-R^{2b})-CH_2-CH_2-O-R^{2b}$, $-N(-CH_2-CH_2-O-R^{2b})_2$, $-N(-R^{2b})-C(=O)-R^{3b}$, $-N(-R^{2b})-S(=O)_2-R^{3b}$, and a 5-6

membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S substituted with 0-4 $R^{1b'}$ groups;

alternatively, when two R^{1b} may be present on adjacent ring atoms of G and combine to form a benzene ring substituted with 0-4 $R^{1b'}$ groups or a 5-6 membered aromatic or non-aromatic heterocyclic ring having 1-3 heteroatoms selected from N, O and S substituted with 0-4 $R^{1b'}$ groups;

in a second alternative, one of the R^{1b} groups of G can cylize with the -N-R^5 group of E to form a 5-7 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, which is subtituted with 0-4 $R^{1b'}$ groups, wherein two of the $R^{1b'}$ groups attached to the same ring carbon may form a (=O) group;

R^{2b} and R^{3b} are independently selected from the group consisting of:

-H, -C_{1-6}alkyl, -C_{1-6}alkyloxy, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-6}alkylC_{3-8}cycloalkyl and -C_{0-6}alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-O^-, -CN, -CF_3 and -NO_2;

$R^{1b'}$ is independently selected from the group consisting of:

halo, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-6}alkylC_{3-8}cycloalkyl, -C_{1-4}alkyl-C(=O)-OH, -CN, -NO_2, -$S(=O)_2$-OH, -N(-$R^{2b'}$, -$R^{3b'}$), -C(=O)-N(-$R^{2b'}$, -$R^{3b'}$), -$S(=O)_2$-N(-$R^{2b'}$, -$R^{3b'}$), -$S(=O)_2$-$R^{2b'}$, -CF_3, -O-$R^{2b'}$, -O-CH_2-CH_2-O-$R^{2b'}$, -O-CH_2-C(=O)-O-$R^{2b'}$, -N(-$R^{2b'}$)-CH_2-CH_2-O-$R^{2b'}$, -N(-CH_2-CH_2-O-$R^{2b'}$)$_2$, -N(-$R^{2b'}$)-C(=O)-$R^{3b'}$ and -N(-$R^{2b'}$)-$S(=O)_2$-$R^{3b'}$;

$R^{2b'}$ and $R^{3b'}$ are independently selected from the group consisting of:

-H, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloakyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, -CF3 and $-NO_2$;

J is selected from the group consisting of:

a direct link, $-S(=O)_2-$, $-C(=O)-$, $-N(-R^7)-S(=O)_2-$, $-C(=O)-N(-R^7)-S(=O)_2-$, $-C(=O)-N(-R^7)-(CH_2)_y-$, $-S(=O)_2-N(-R^7)$ $-(CH_2)_y-$, and $-N(-R^7)-C(=O)-(CH_2)_y-$;

y is an integer of 0-2;

R^7 is selected from the group consisting of:

-H, $-C_{2-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl, $-C_{1-6}$alkyl-C(=O)-OH, $-C_{1-6}$alkyl-OH, $-C_{1-6}$alkyl-O-C_{1-4}alkyl, $-C_{0-4}$alkyl-(carbocyclic aryl), $-C_{0-4}$alkyl-(monocyclic or bicyclic heterocyclic ring system having from 0-4 heteroatoms selected from the group consisting of N, O and S), $-CH_2-C(=O)-O-C_{1-4}$alkyl and $-CH_2-C(=O)-O-C_{1-4}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety or the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2-OH$, -CN, $-CF_3$ and $-NO_2$;

X is selected from the group consisting of:

phenyl, which is substituted with 0-3 R^{1c} groups;

naphthyl, which is substituted with 0-3 R^{1c} groups;

a 6-membered heteroaromatic ring containing from 1-2 nitrogen atoms, wherein the ring is substituted with 0-3 R^{1c} groups; and

a fused heterobicyclic ring system, wherein the ring system contains 1-3 heteroatoms selected from N, O and S and is substituted with 0-3 R^{1c} groups;phenyl, which is substituted with 0-3 R^{1c} groups;

R^{1c} is independently selected from the group consisting of:

halo, $-CF_3$, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl, $-C_{1-4}$alkyl-C(=O)-OH, $-CF_3$, -CN, $-NO_2$, $-(CH_2)_z$-N($-R^{2c}$, $-R^{3c}$), -C(=O)-N($-R^{2c}$, $-R^{3c}$), -C(=NH)-N($-R^{2c}$, $-R^{3c}$), -C(=NMe)-N($-R^{2c}$, $-R^{3c}$), $-S(=O)_2$-N($-R^{2c}$, $-R^{3c}$), $-S(=O)_2-R^{2c}$, $-S(=O)_2$-O H, $-CF_3$, $-O-R^{2c}$, $-O(-CH_2)_z-O-R^{2c}$, $-O(-CH_2)_z$-C(=O)-O-R^{2c}, -N($-R^{2c}$), $-O(-CH_2)_z-O-R^{2c}$, $-N[(-CH_2)_z-O-R^{2c}]_2$, $-(CH_2)_z$-N($-R^{2c}$)-C(=O)-R^{3c}, $-(CH_2)_z$-N($-R^{2c}$)-$S(=O)_2-R^{3c}$, and a 5-6 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

z is an integer of 0-4;

R^{2c} and R^{3c} are independently selected from the group consisting of:

-H, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-S(=O)_2$-OH, -CN, $-CF_3$ and $-NO_2$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention also provides a compound of the formula (I):

A-Q-D-E-G-J-X

wherein:

A is selected from the group consisting of:

$-C_{1-6}$alkyl and $-C_{3-8}$cycloalkyl;

phenyl, which is substituted with 0-2 R^1 groups;

naphthyl, which is substituted with 0-2 R^1 groups; and

a 3-10 membered aromatic or non-aromatic heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and is substituted with 0-2 R^1 groups;

R^1 is independently selected from the group consisting of:

halo, $-C_{1-4}$alkyl, -CN, $-NO_2$, $-(CH_2)_m-N(-R^2,-R^3)$, $-C(=O)-N(-R^2,-R^3)$, $-S(=O)_2-N(-R^2,-R^3)$, $-S(=O)_2-R^2$, $-(CH_2)_m-C(=NR^3)-R^2$, $-(CH_2)_m-C(=NR^2)-N(R^2,R^3)$, $-(CH_2)_m-N(R^2)-C(=NR^2)-N(R^2,R^3)$, $-CF_3$, $-(CH_2)_m-O-R^2$ and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^2 and R^3 are independently selected from the group consisting of:

-H, $-C_{1-4}$alkyl and $-C_{0-4}$alkyl-(carbocyclic aryl);

m is an integer of 0-2;

Q is selected from the group consisting of:

a direct link, $-C_{1-4}$alkyl, $-C_{2-4}$alkenyl, $-C_{2-4}$alkynyl, -C(=O)-, -C(=NH)-, -C(=NMe)-, $-N(-R^4)-$, $-N(-R^4)-CH_2-$, -NH-C(=NH)-, -NH-C(=NMe)-, $-C(=O)-N(-R^4)-$, $-N(-R^4)-C(=O)-$, $-S(=O)_2-$, -O-, $-S(=O)_2-N(-R^4)-$ and $-N(-R^4)-S(=O)_2$;

R^4 is selected from the group consisting of:

-H, $-C_{1-4}$alkyl and $-C_{0-4}$alkyl-(carbocyclic aryl);

D is selected from the group consisting of:

a direct link;

phenyl, which is substituted with 0-2 R^{1a} groups; and

a 5-10 membered aromatic or non-aromatic heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and the ring system is substituted with 0-2 R^{1a} groups;

R^{1a} is independently selected from the group consisting of:

halo, $-C_{1-4}$alkyl, -CN, $-NO_2$, $-(CH_2)_n-N(-R^{2a}, -R^{3a})$, $-S(=O)_2-N(-R^{2a}, -R^{3a})$, $-S(=O)_2-R^{2a}$, $-CF_3$, $-(CH_2)_n-OR^{2a}$, $-C(=O)-O-R^{2a}$, $-C(=O)-N(-R^{2a}, -R^{3a})$ and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

n is an integer of 0-2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

-H, $-C_{1-4}$alkyl, and $-C_{1-4}$alkyl-(carbocyclic aryl);

E is selected from the group consisting of:

a direct link, $-(CH_2)_q-C(=O)-$, $-(CH_2)_q-N(-R^5)-C(=O)-(CH_2)_x-$, $-(CH_2)_q-C(=O)-N(-R^5)-(CH_2)_x-$, $-(CH_2)_q-N(-R^5)-(CH_2)_x-$, $-(CH_2)_q-N(R^5)CO-NR^6(CH_2)_x-$ and $-SO_2-$;

q and x are independently an integer of 0-2;

R^5 and R^6 are independently selected from the group consisting of:

-H, $-C_{1-4}$alkyl, $-C_{0-4}$alkyl-(carbocyclic aryl),

$-C_{0-4}$alkyl-(monocyclic heteroaryl), $-C_{1-4}$alkyl-C(=O)-OH and

-C_{1-4}alkyl-C(=O)-O-C_{1-4}alkyl;

G is selected from the group consisting of:

phenyl, which is substituted with 0-2 R^{1b} groups; and

a 5-6 membered aromatic heterocyclic ring containing 1-4 hetero atoms selected from O, S and N, wherein the heterocyclic ring is substituted with 0-2 R^{1b} groups;

R^{1b} is independently selected from the group consisting of:

halo, -C_{1-4}alkyl, -CN, -NO_2, -N(-R^{2b}, -R^{3b}), -C(=O)-N(-R^{2b}, -R^{3b}), -S(=O)$_2$-N(-R^{2b}, -R^{3b}), -S(=O)$_2$-R^{2b}, -CF_3, -O-R^{2b}, -O-CH_2-CH_2-O-R^{2b}, -O-CH_2-C(=O)-O-R^{2b}, -N(-R^{2b})-CH_2-CH_2-O-R^{2b}, -N(-CH_2-CH_2-O-R^{2b})$_2$, -N(-R^{2b})-C(=O)-R^{3b}, -N(-R^{2b})-S(=O)$_2$-R^{3b} and a 5-6 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

alternatively, when two R^{1b} may be present on adjacent ring atoms of G and combine to form a benzene ring substituted with 0-4 $R^{1b'}$ groups or a 5-6 membered aromatic or non-aromatic heterocyclic ring having 1-3 heteroatoms selected from N, O and S substituted with 0-4 $R^{1b'}$ groups;

in a second alternative, one of the R^{1b} groups of G can cylize with the -N-R^5 group of E to form a 5-7 membered saturated, unsaturated or partially unsaturated heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, which is substituted with 0-4 $R^{1b'}$ groups, wherein two of the $R^{1b'}$ groups attached to the same ring carbon may form a (=O) group;

R^{2b} and R^{3b} are independently selected from the group consisting of:

-H, -C_{1-4}alkyl and -C_{1-4}alkyl-(carbocyclic aryl);

$R^{1b'}$ is independently selected from the group consisting of:

halo, -C_{1-4}alkyl, -CN, -NO_2, -N(-$R^{2b'}$, -$R^{3b'}$), -C(=O)-N(-$R^{2b'}$, -$R^{3b'}$), -S(=O)$_2$-N(-$R^{2b'}$, -$R^{3b'}$), -S(=O)$_2$-$R^{2b'}$, -CF_3, -O-$R^{2b'}$, -O-CH_2-CH_2-O-$R^{2b'}$,

$-O-CH_2-C(=O)-O-R^{2b'}$, $-N(-R^{2b'})-CH_2-CH_2-O-R^{2b'}$, $-N(-CH_2-CH_2-O-R^{2b'})_2$, $-N(-R^{2b'})-C(=O)-R^{3b'}$, $-N(-R^{2b'})-S(=O)_2-R^{3b'}$;

$R^{2b'}$ and $R^{3b'}$ are independently selected from the group consisting of:

-H, $-C_{1-4}$alkyl and $-C_{1-4}$alkyl-(carbocyclic aryl);

J is selected from the group consisting of:

a direct link, $-S(=O)_2-$, $-C(=O)-$, $-N(-R^7)-S(=O)_2-$, $-C(=O)-N(-R^7)-S(=O)_2-$, $-C(=O)-N(-R^7)-(CH_2)_y-$, $-S(=O)_2-N(-R^7)-$, $-(CH_2)_y-$ and $-N(-R^7)-C(=O)-(CH_2)_y-$;

y is an integer of 0-2;

R^7 is selected from the group consisting of:

-H, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{0-4}$alkyl-(carbocyclic aryl), $-C_{0-4}$alkyl-(heterocyclic ring system), $-CH_2-C(=O)-O-C_{1-4}$alkyl and $-CH_2-C(=O)-O-C_{1-4}$alkyl-(carbocyclic aryl);

X is selected from the group consisting of:

phenyl, which is substituted with 0-3 R^{1c} groups;

naphthyl, which is substituted with 0-3 R^{1c} groups;

a 6-membered heteroaromatic ring containing from 1-2 nitrogen atoms, wherein the ring is substituted with 0-3 R^{1c} groups; and

a fused heterobicyclic ring system, wherein the ring system contains 1-3 heteroatoms selected from N, O and S and is substituted with 0-3 R^{1c} groups;

R^{1c} is independently selected from the group consisting of:

halo, $-C_{1-4}$alkyl, -CN, $-NO_2$, $-(CH_2)_z-N(-R^{2c}, -R^{3c})$, $-C(=O)-N(-R^{2c}, -R^{3c})$, $-C(=NH)-N(-R^{2c}, -R^{3c})$, $-C(=NMe)-N(-R^{2c}, -R^{3c})$, $-S(=O)_2-N(-R^{2c}, -R^{3c})$, $-S(=O)_2-R^{2c}$, $-S(=O)_2-O^-$, $-CF_3$, $-O-R^{2c}$, $-O-CH_2-CH_2-O-R^{2c}$, $-O-CH_2-C(=O)-O-R^{2c}$, $-N(-R^{2c})-CH_2-CH_2-O-R^{2c}$, $-N(-CH_2-CH_2-O-R^{2c})_2$,

$-(CH_2)_z-N(-R^{2c})-C(=O)-R^{3c}$, $-(CH_2)_z-N(-R^{2c})-S(=O)_2-R^{3c}$, and a 5-6 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

z is an integer of 0-2;

R^{2c} and R^{3c} are independently selected from the group consisting of:

-H, $-C_{1-4}$alkyl and $-C_{1-4}$alkyl-(carbocyclic aryl);

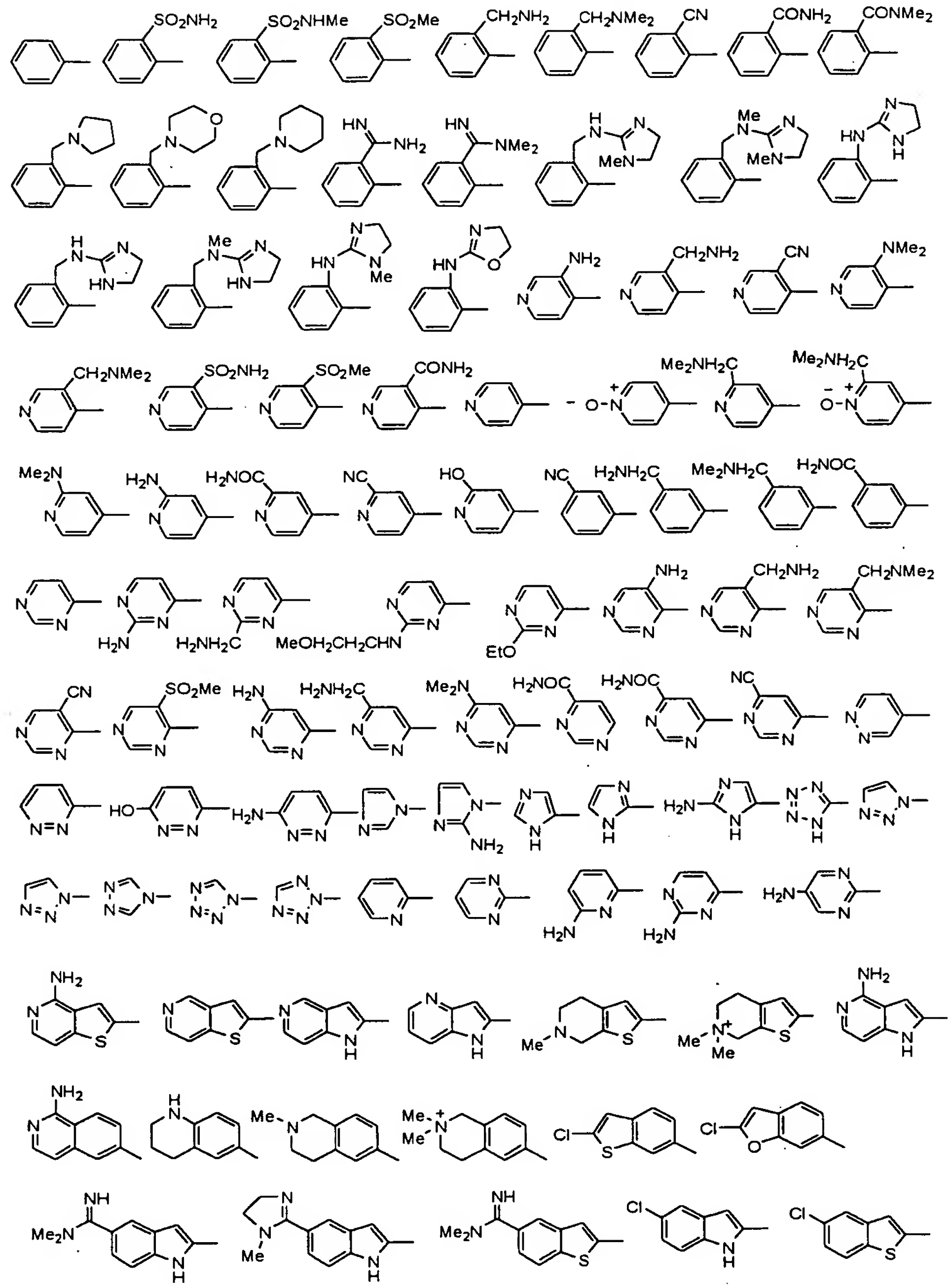
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, thereof.

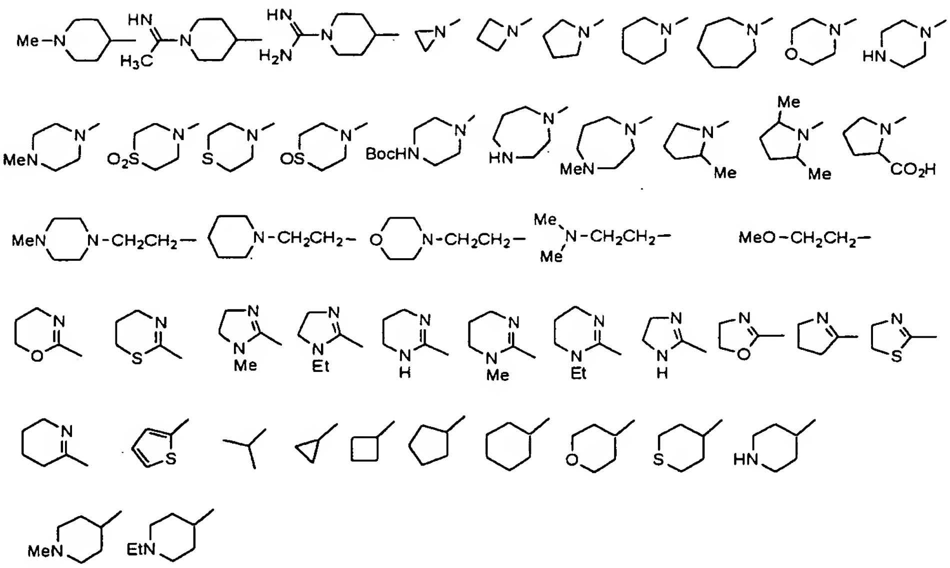
The present invention also provides compounds of the formula (I):

A-Q-D-E-G-J-X

wherein:

A is selected from the group consisting of:

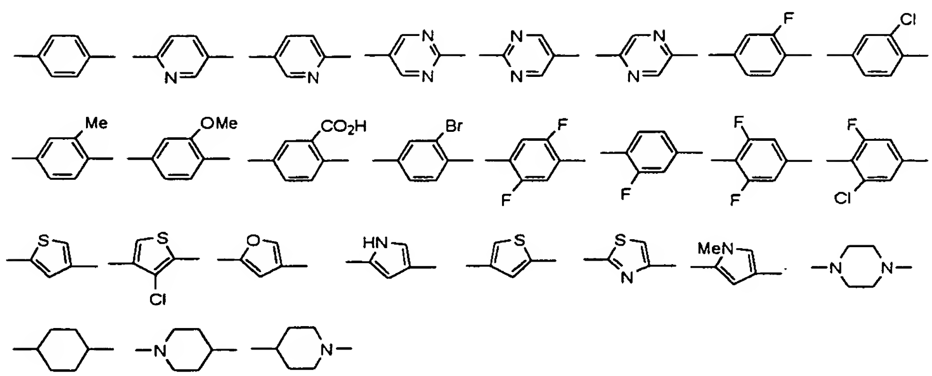




Q is selected from the group consisting of:

a direct link, -C(=NH), -C(=NMe)-, -C(=O)-, $-CH_2-$, -NH-, $-N(-CH_3)-$, -O-, $-NH-CH_2-$, $-CH_2-NH-$, $-N(-CH_3)-CH_2-$, and $-CH_2-N(-CH_3)-$;

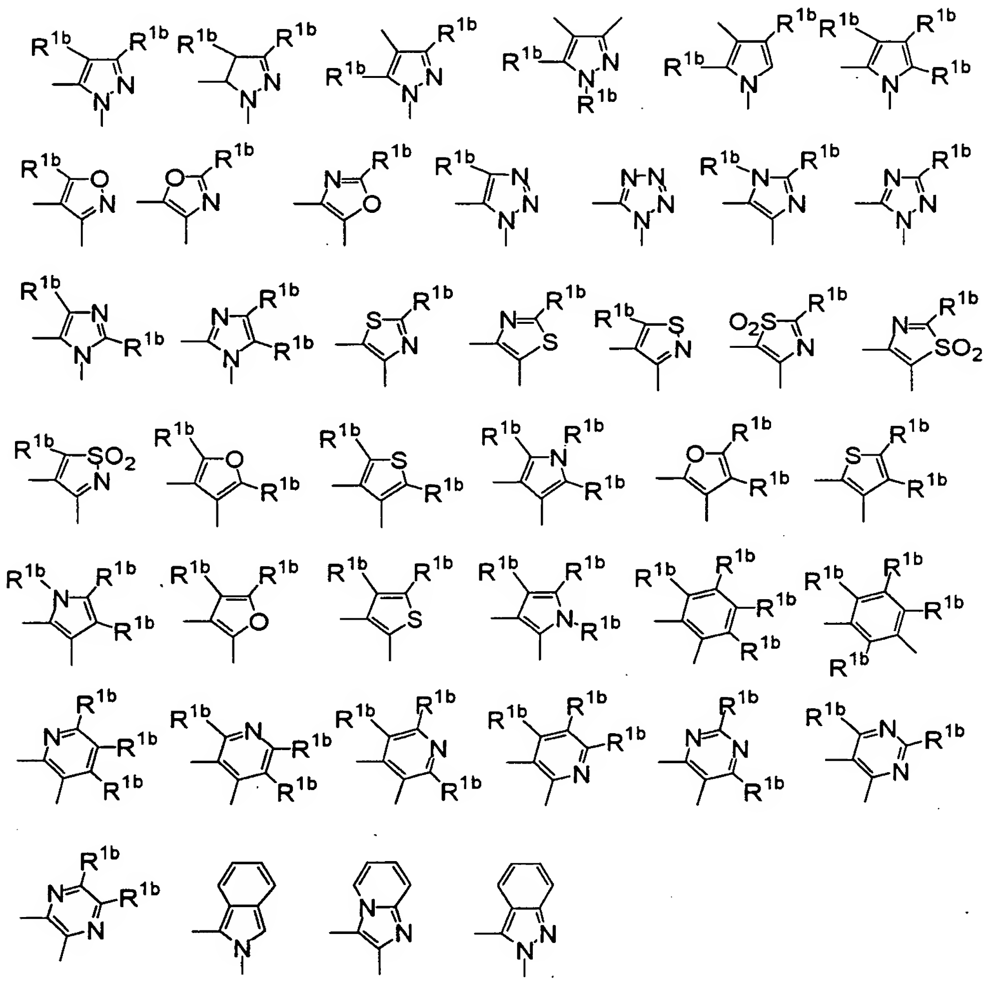
D is selected from the group consisting of:



E is selected from the group consisting of:

a direct link, -NH-C(=O)-, -N(-CH_3)-C(=O)-, -N(-CH_2CO_2H)-C(=O)-, -C(=O)-NH-, -C(=O)-N(-CH_3)-, -NH-CH_2- and –CH_2-NH-;

G is selected from the group consisting of:



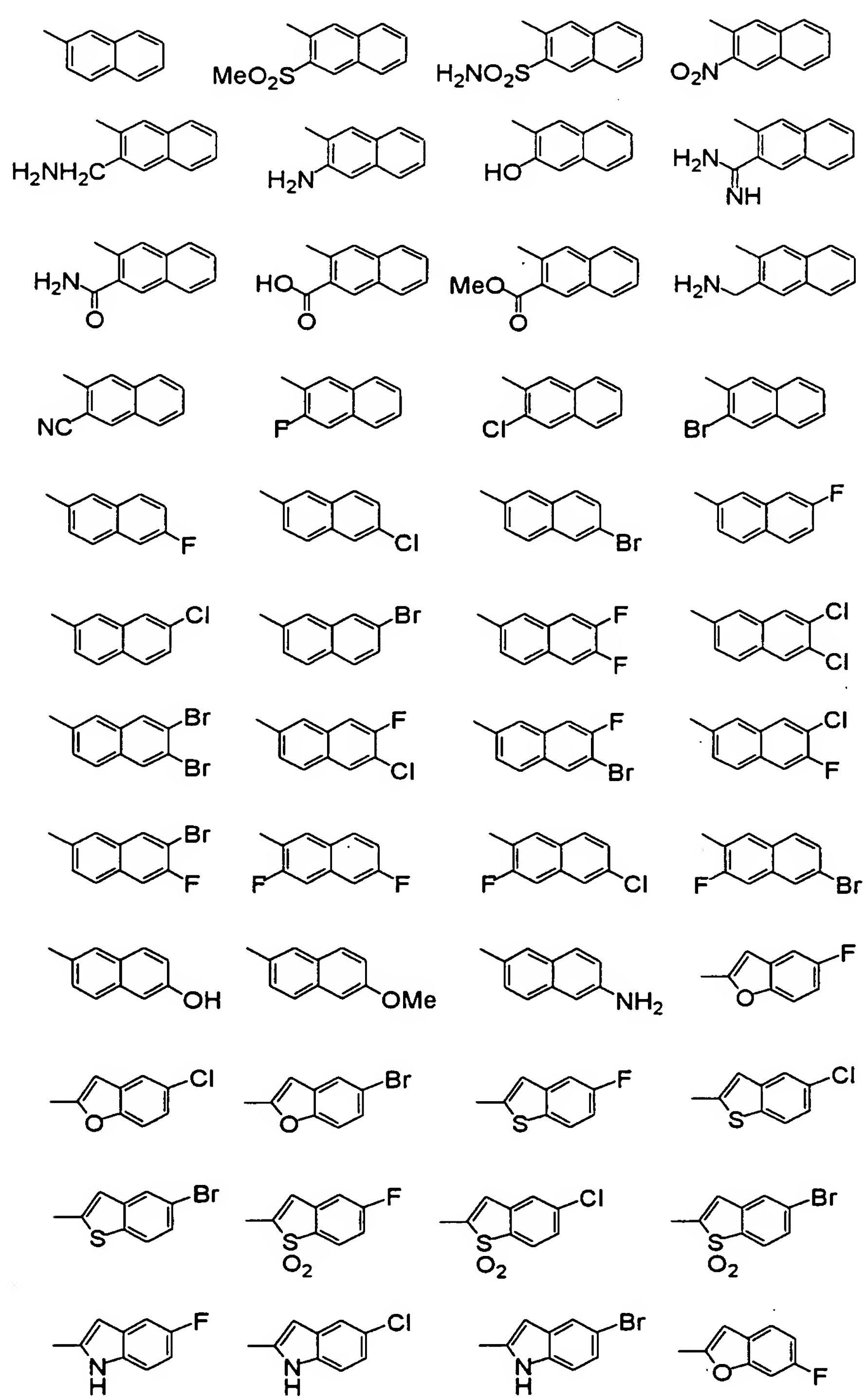
R^{1b} is selected from the group consisting of:

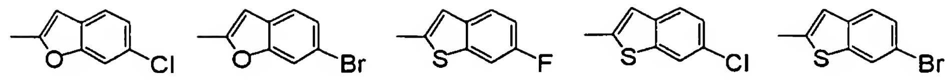
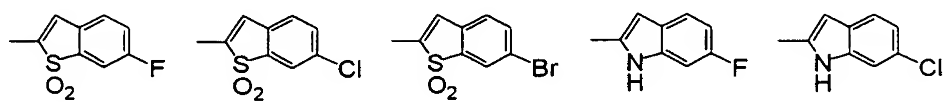
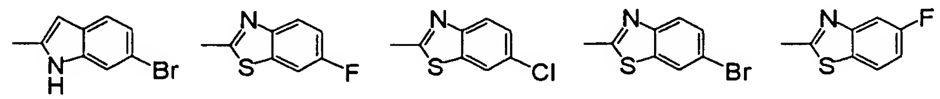
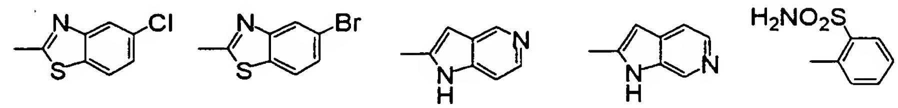
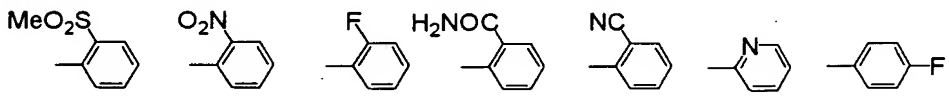
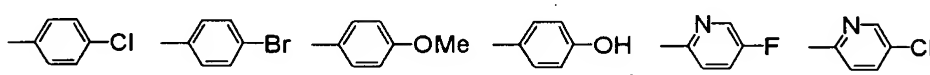
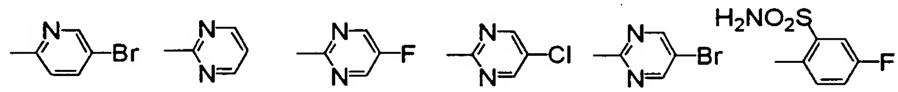
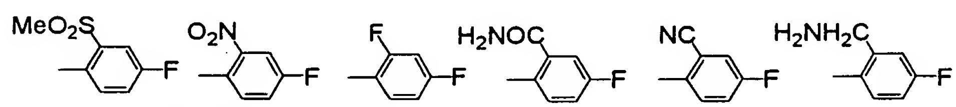
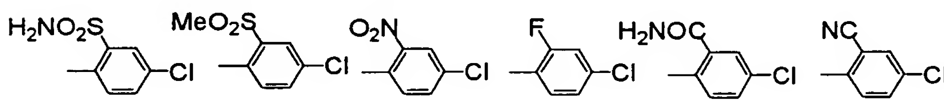
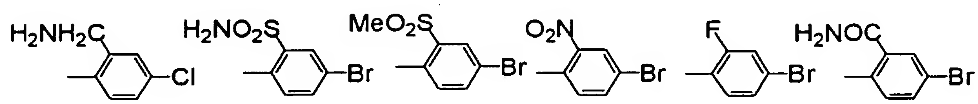
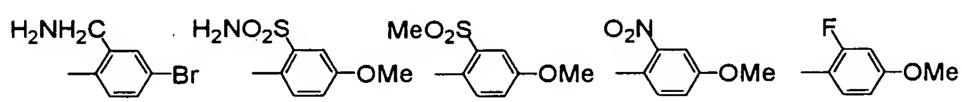
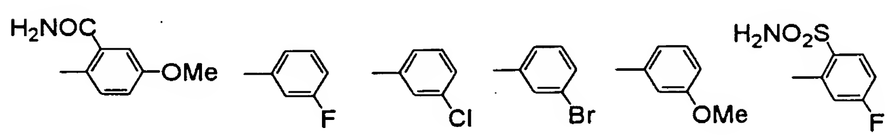
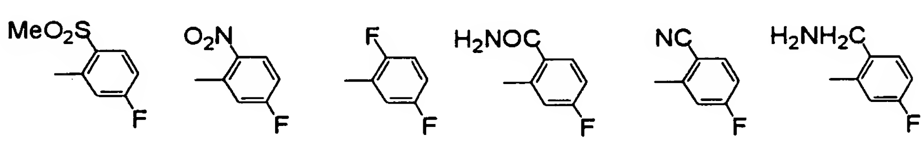
-H, -Me, $-CF_3$, -F, -Cl, -Br, $-SO_2Me$, -CN, $-CONH_2$, $-CONMe_2$, $-NH_2$, $-NO_2$, -NHCOMe, $-NHSO_2Me$, $-CH_2NH_2$ and $-CO_2H$;

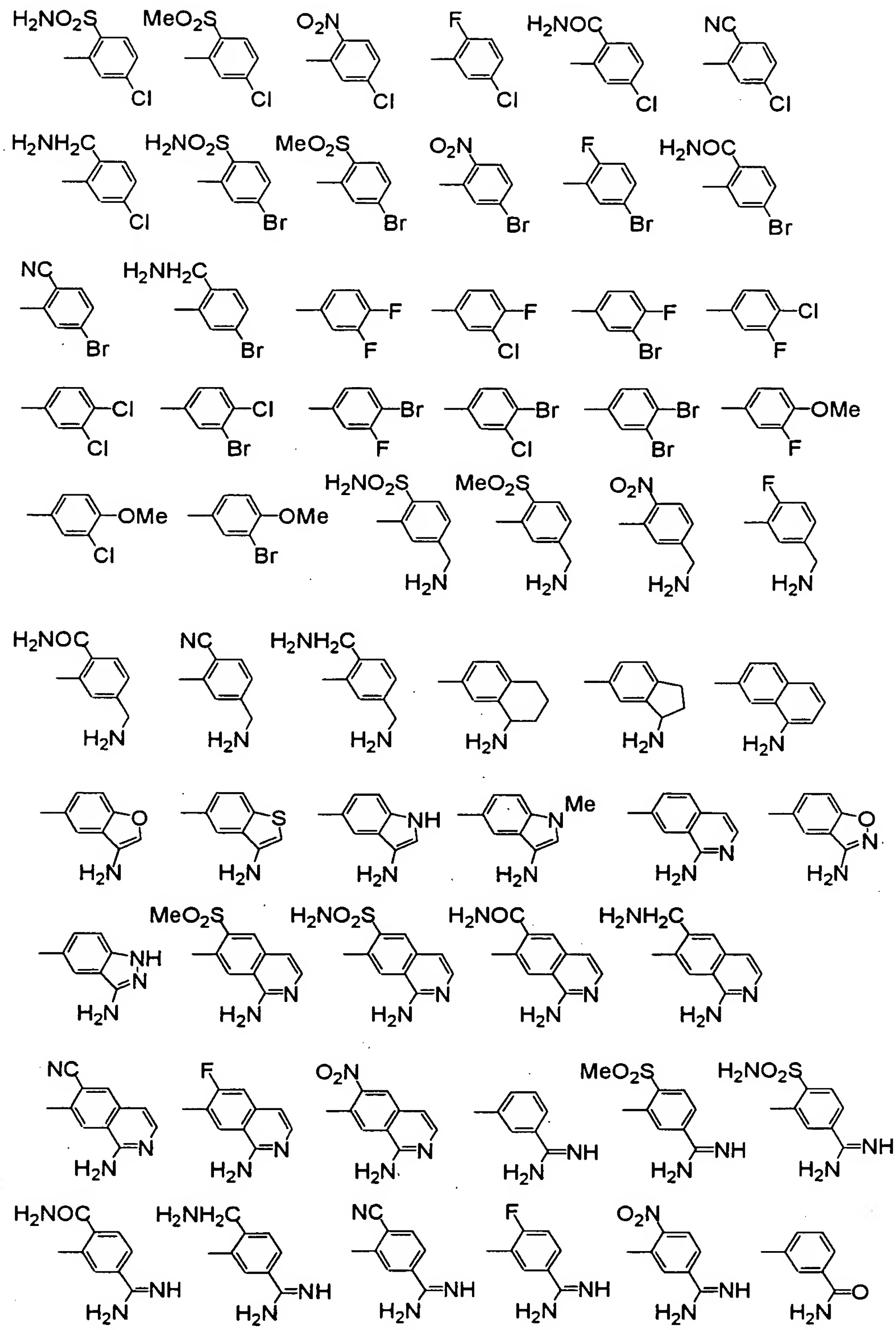
J is selected from the group consisting of:

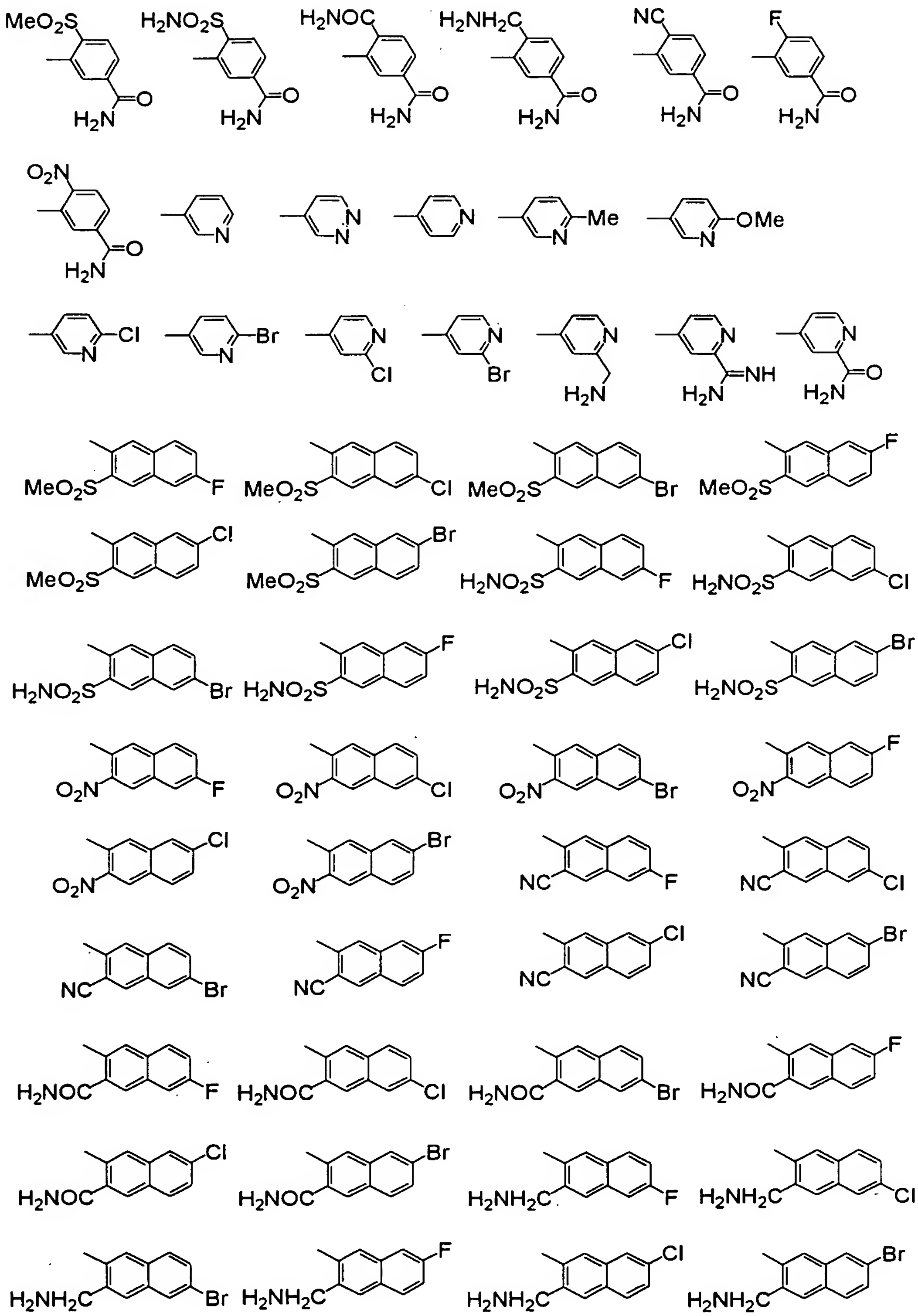
a direct link, -NH-, -O-, -S(=O)$_2$-, -S(=O)$_2$-NH, -NH-S(=O)$_2$-, -C(=O)-, -NH-C(=O)- and -C(=O)-NH-;

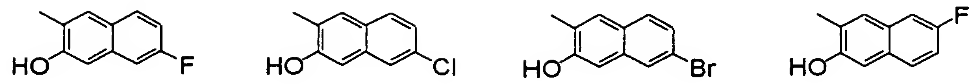
X is selected from the group consisting of:

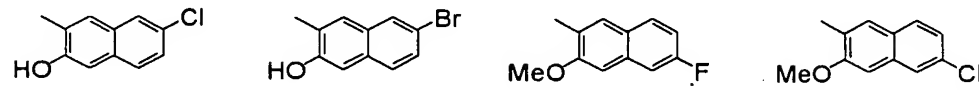


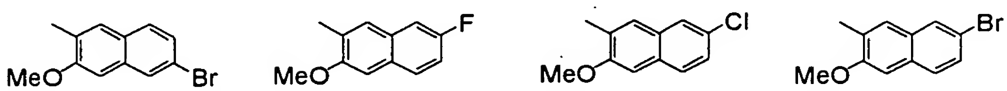














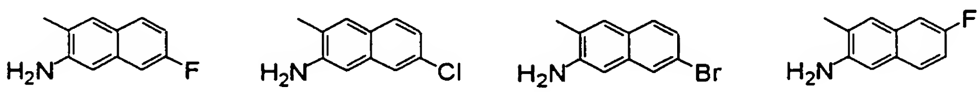


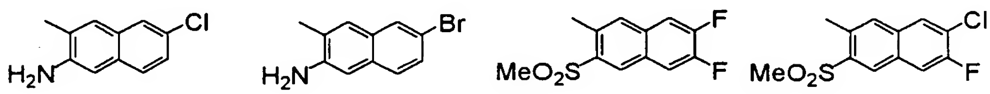


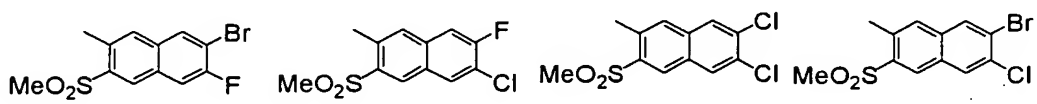


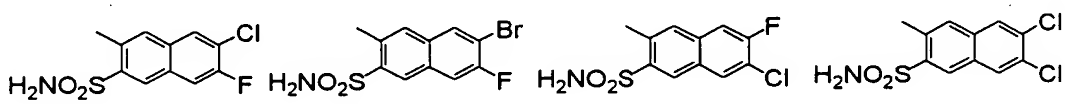


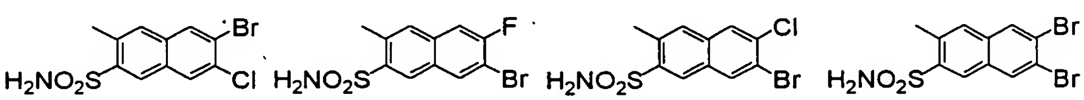


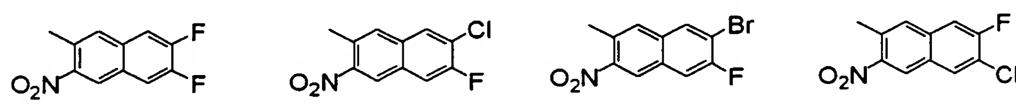


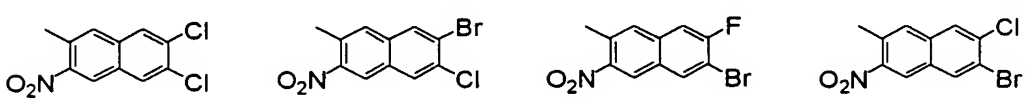


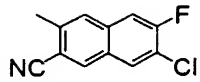
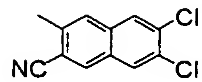
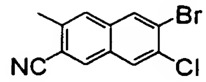
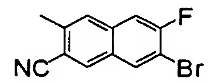


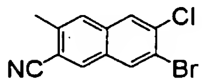
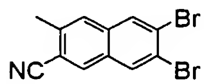
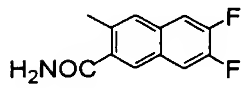
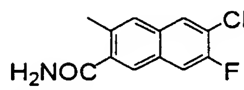


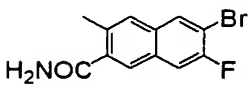
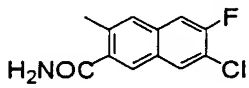
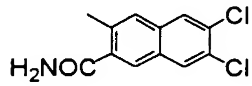
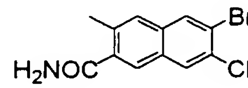


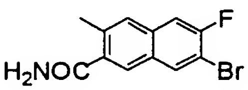
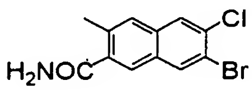
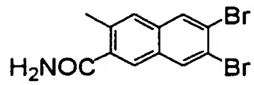
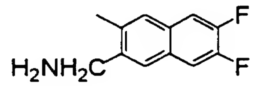


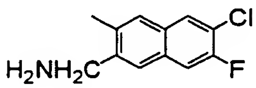
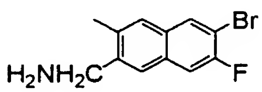
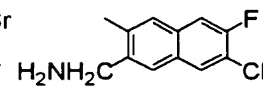
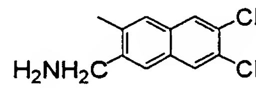


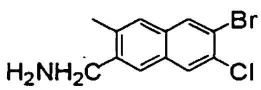
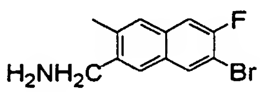
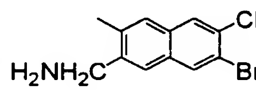
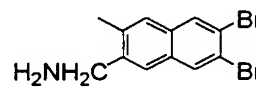
   

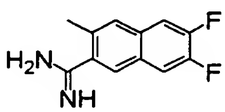
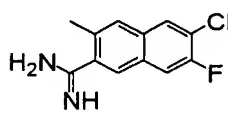
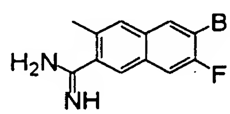
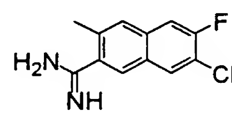
   

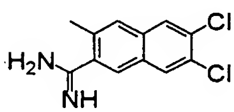
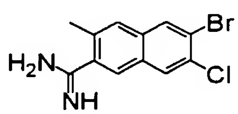
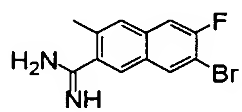
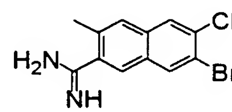
   

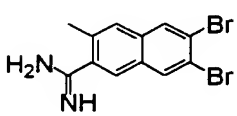
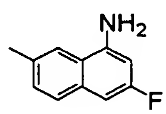
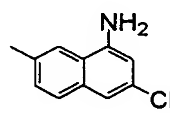
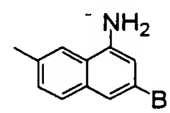
   

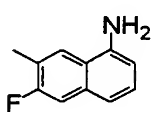
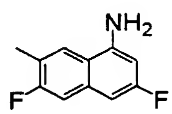
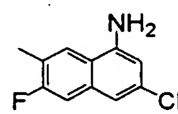
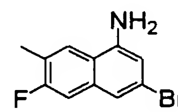
   

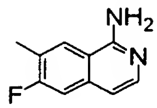
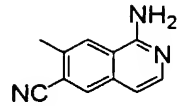
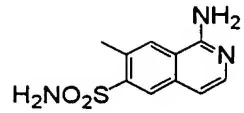
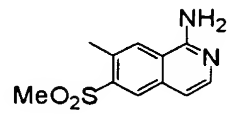
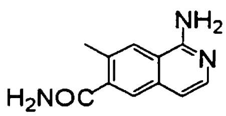
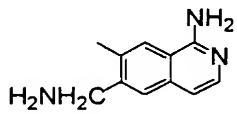
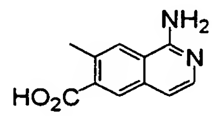
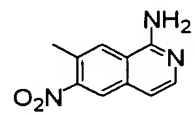
   

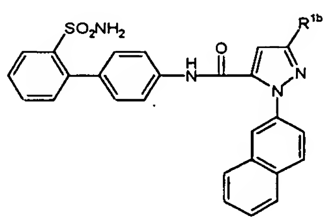
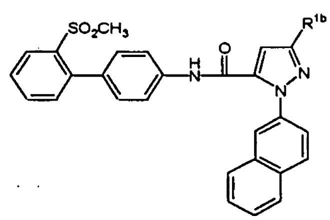
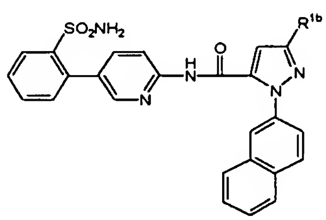
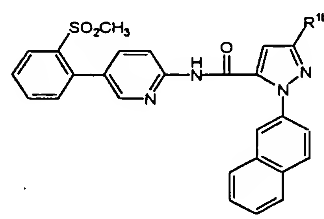
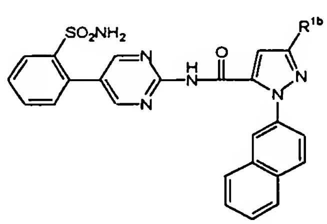
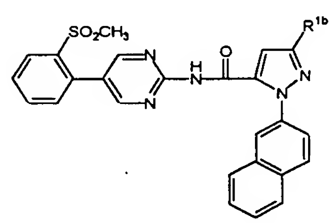
   

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, thereof.

The compounds listed in the following tables are an embodiment of the present invention:

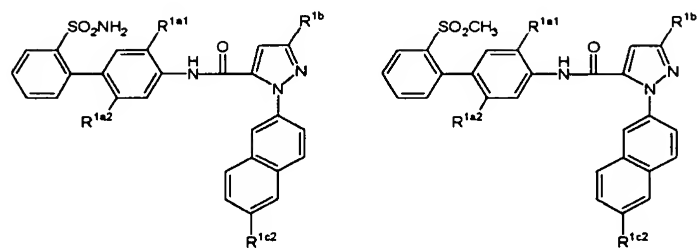
Table 1

wherein:

R^{1b} is selected from the group consisting of –H, -CH_3 and –CF_3.

Table 2



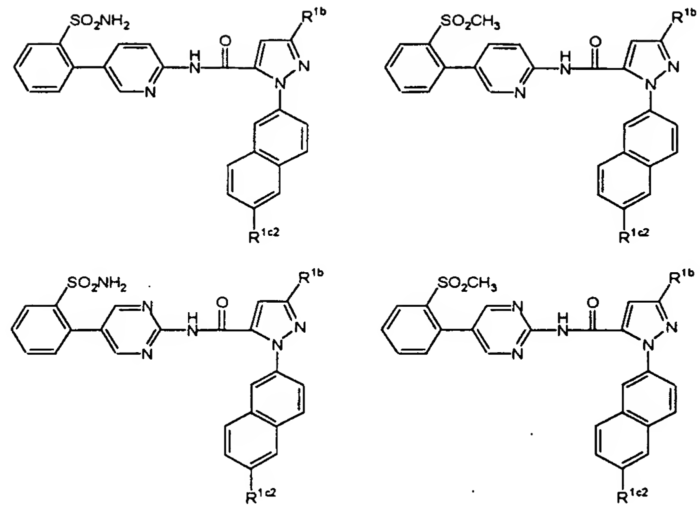
wherein:

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of –H, -CH_3 and CF_3;

R^{1c2} is selected from the group consisting of -H, -F, -Cl, -Br, -OH, -OCH_3 and –NH_2.

Table 3

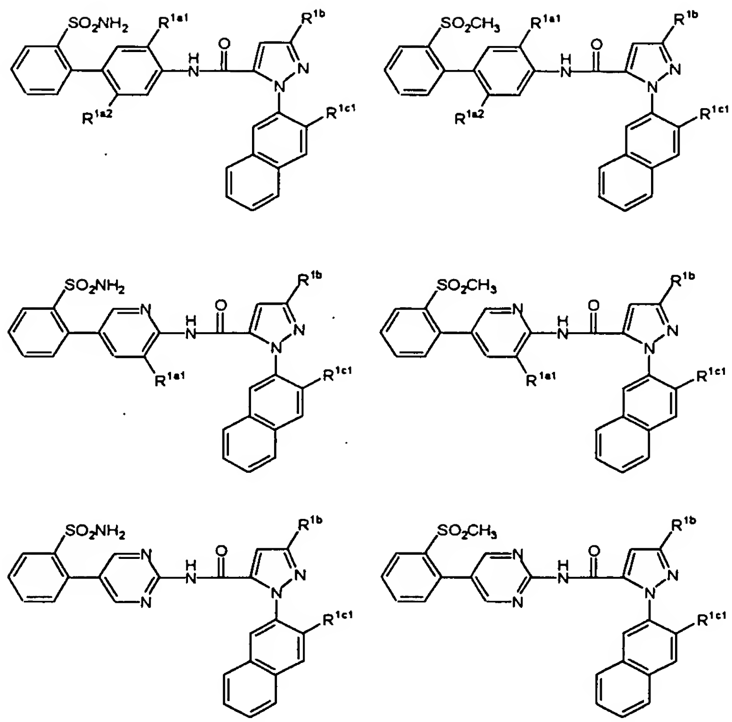


wherein:

R^{1b} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1c2} is selected from the group consisting of -H, -F, -Cl, -Br, -OH, -OCH_3 and –NH_2.

Table 4



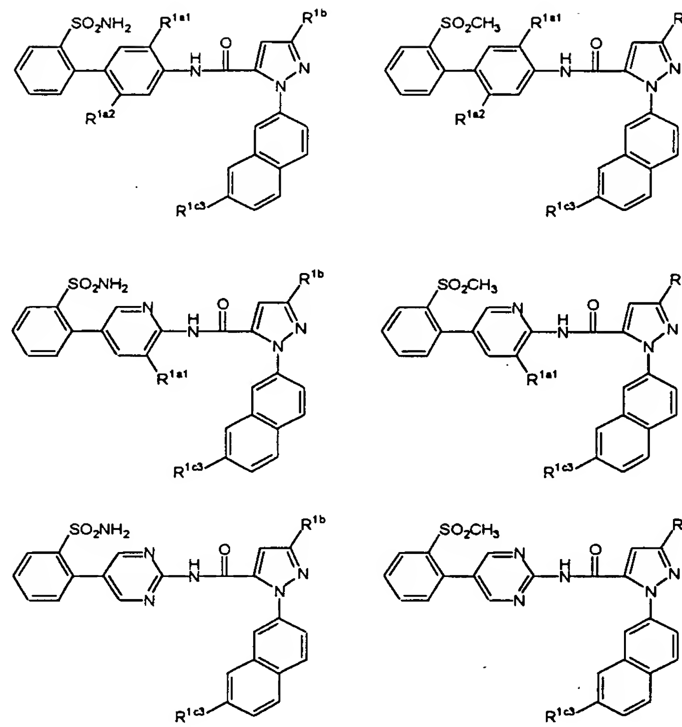
wherein:

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$.

Table 5



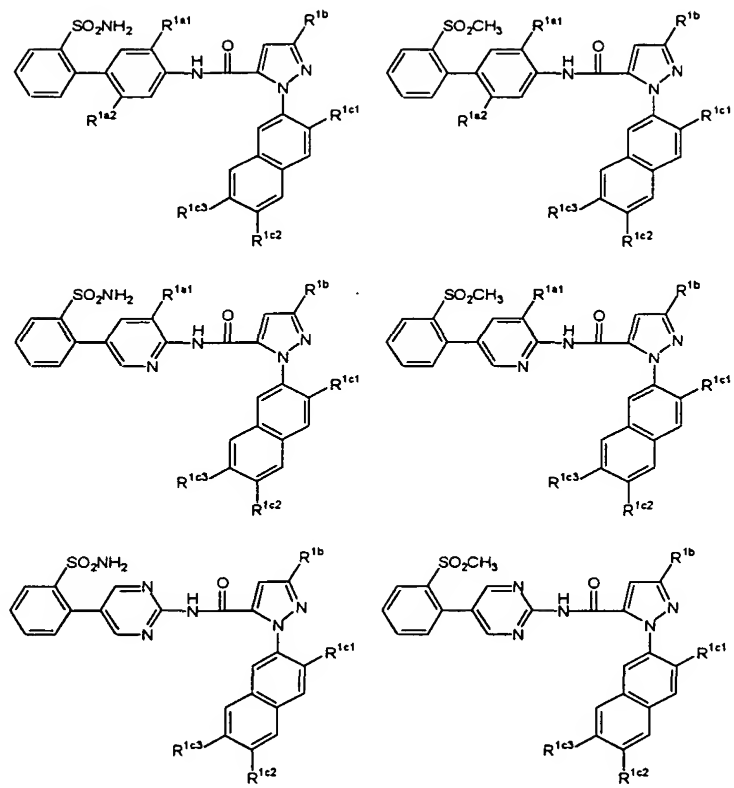
wherein:

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1c3} is selected from the group consisting of -H, -F, -Cl, -Br, -OH, $-OCH_3$ and $-NH_2$.

Table 6



wherein:

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

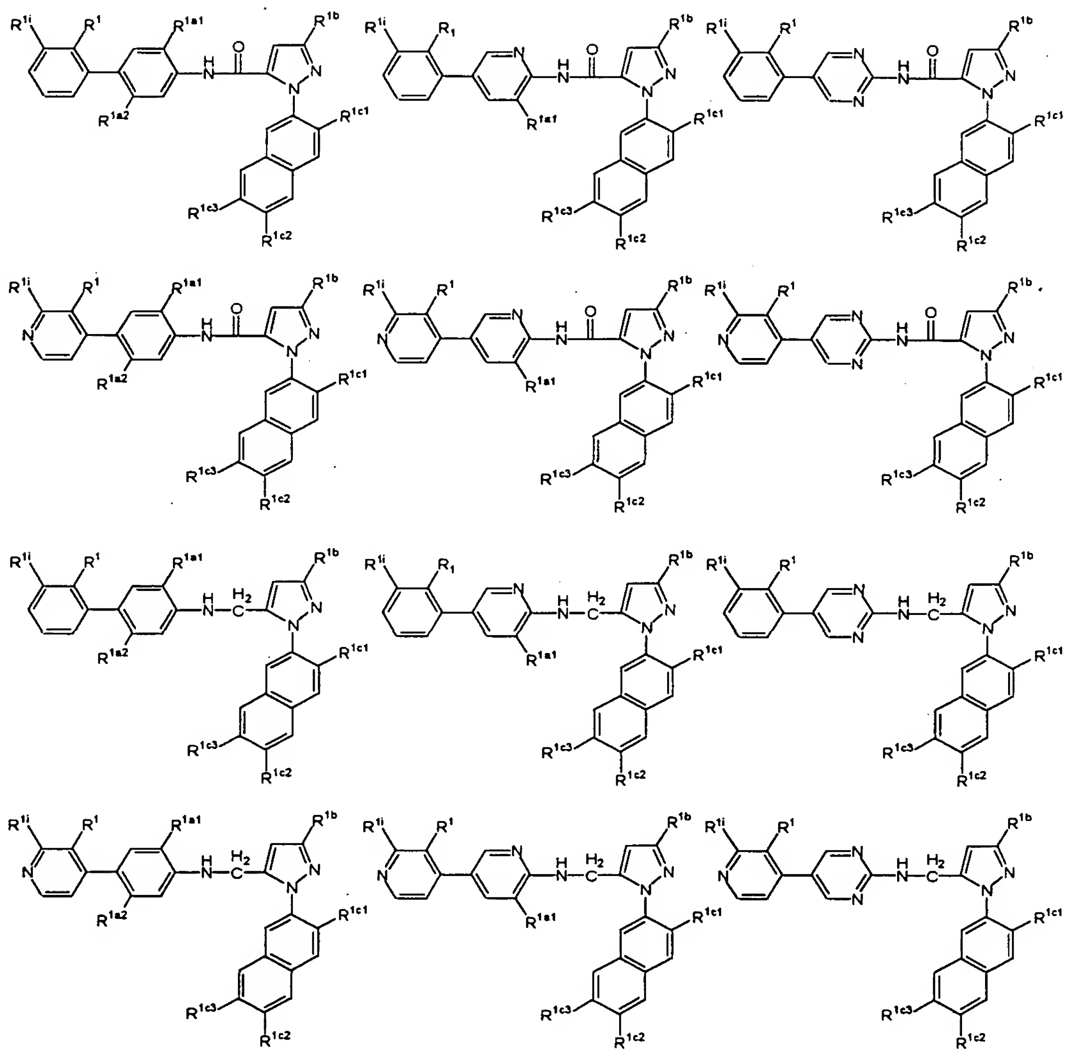
R^{1b} is selected from the group consisting of –H, –CH_3, -CF_3, -CH_2CH_3, -CF_2CF_3, -CH_2NH_2, -$CONH_2$, -SO_2CH_3, -SO_2NH_2, –NH_2COCH_3 and –NH_2COCF_3;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2.

Table 7



wherein:

R^1 is selected from the group consisting of –H, –NH_2, -SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

R^{1i} is selected from the group consisting of –H, –NH_2, -SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

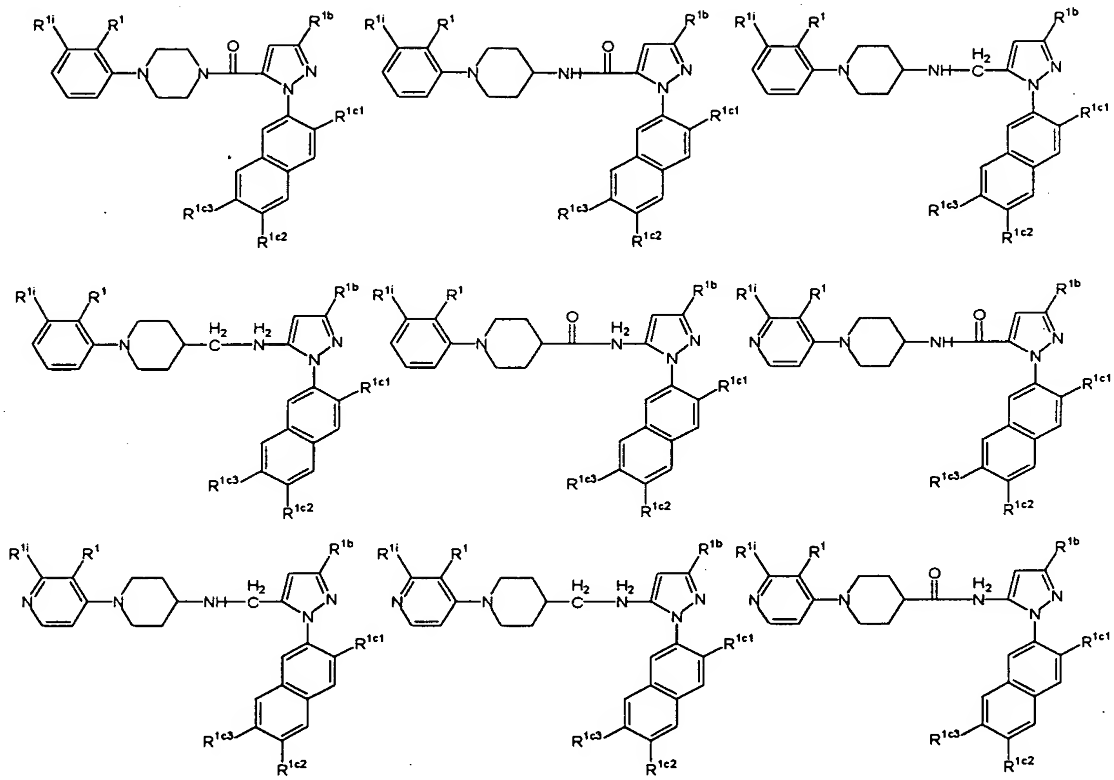
R^{1b} is selected from the group consisting of –H, –CH_3, -CF_3, -CH_2CH_3, -CF_2CF_3, -CH_2NH_2, -$CONH_2$, -SO_2CH_3, -SO_2NH_2, –NH_2COCH_3 and –NH_2COCF_3;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2.

Table 8



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1i} is selected from the group consisting of $-H$, $-NH_2$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

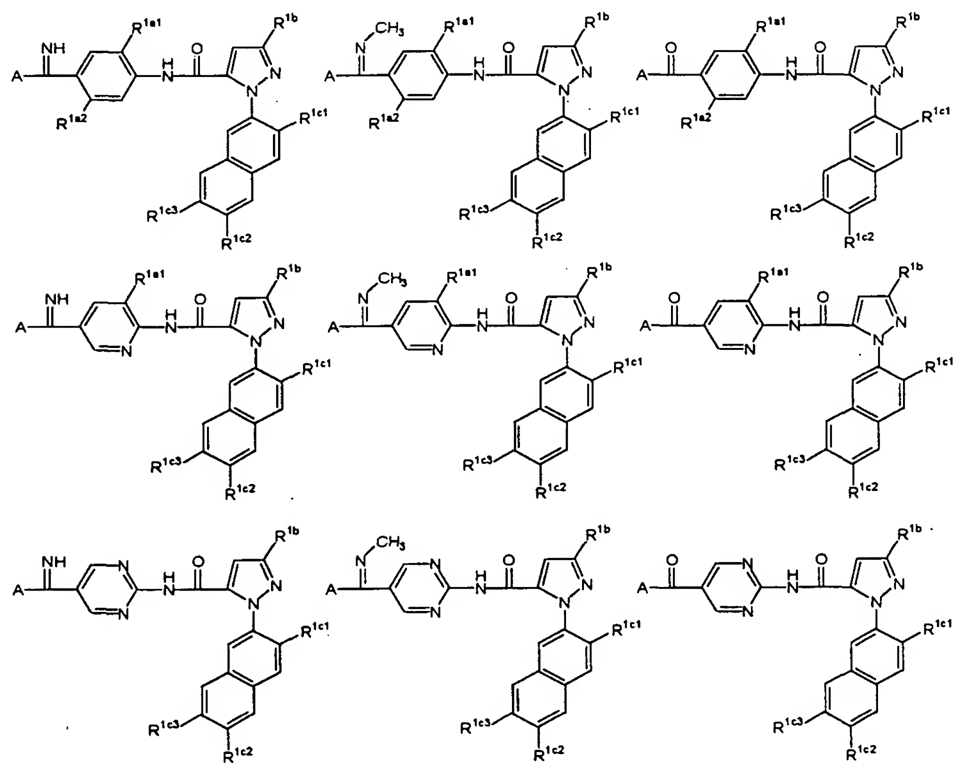
R^{1b} is selected from the group consisting of $-H$, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

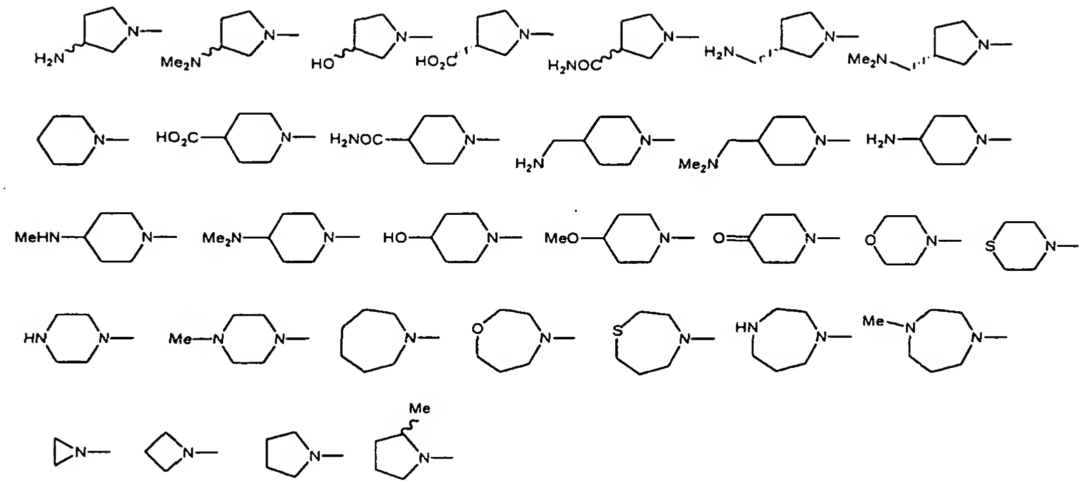
R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$.

Table 9



wherein:

A is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

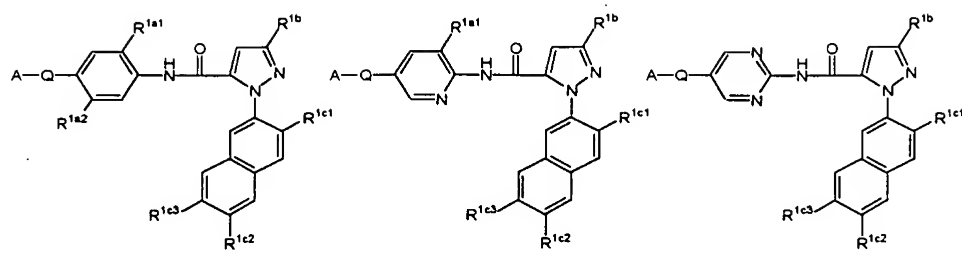
R^{1b} is selected from the group consisting of –H, $-CH_3$, $-CF_3$, $-CH_2CH_3$, $-CF_2CF_3$, $-CH_2NH_2$, $-CONH_2$, $-SO_2CH_3$, $-SO_2NH_2$, $-NH_2COCH_3$ and $-NH_2COCF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

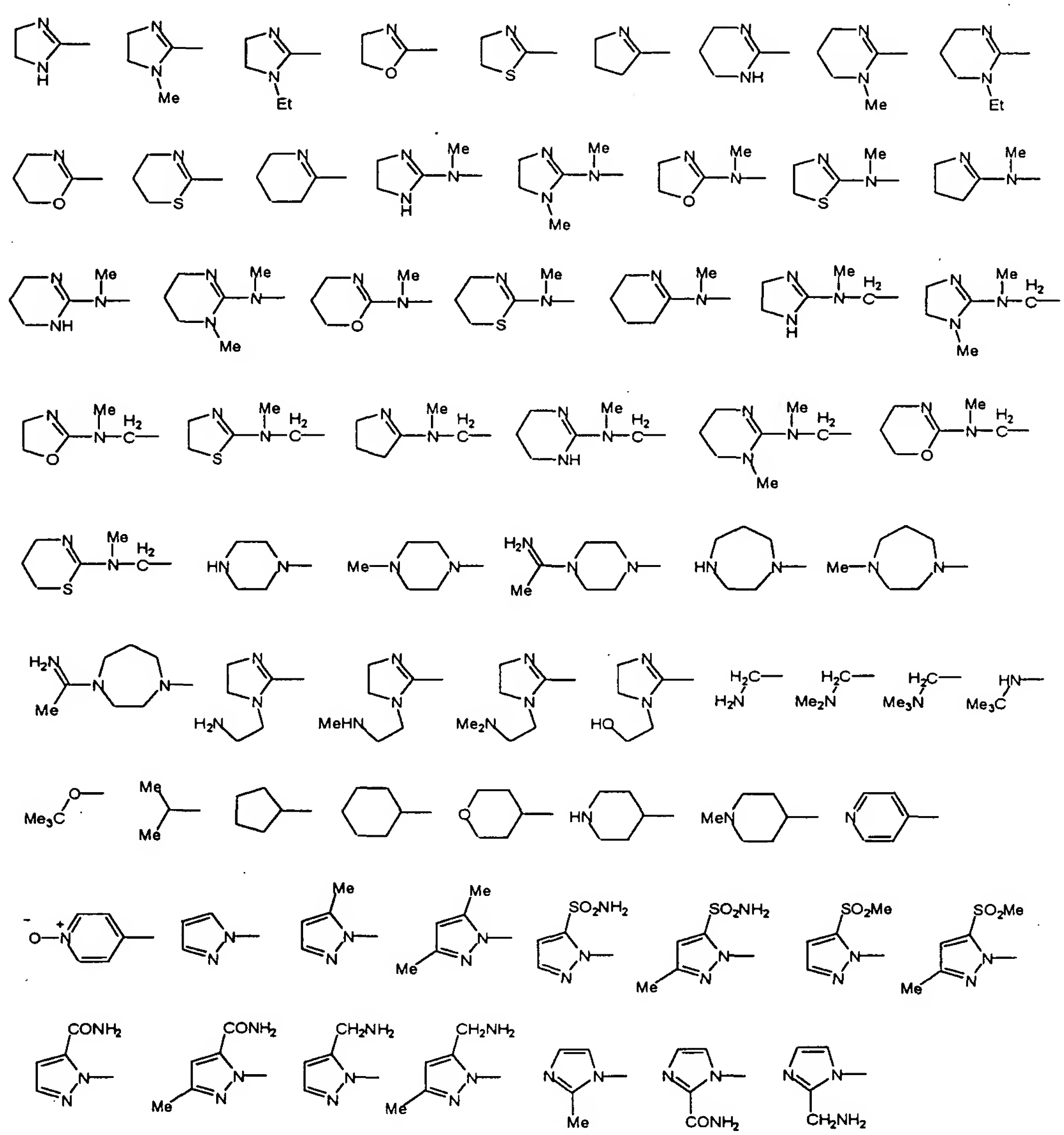
R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$.

Table 10



wherein:

A-Q is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

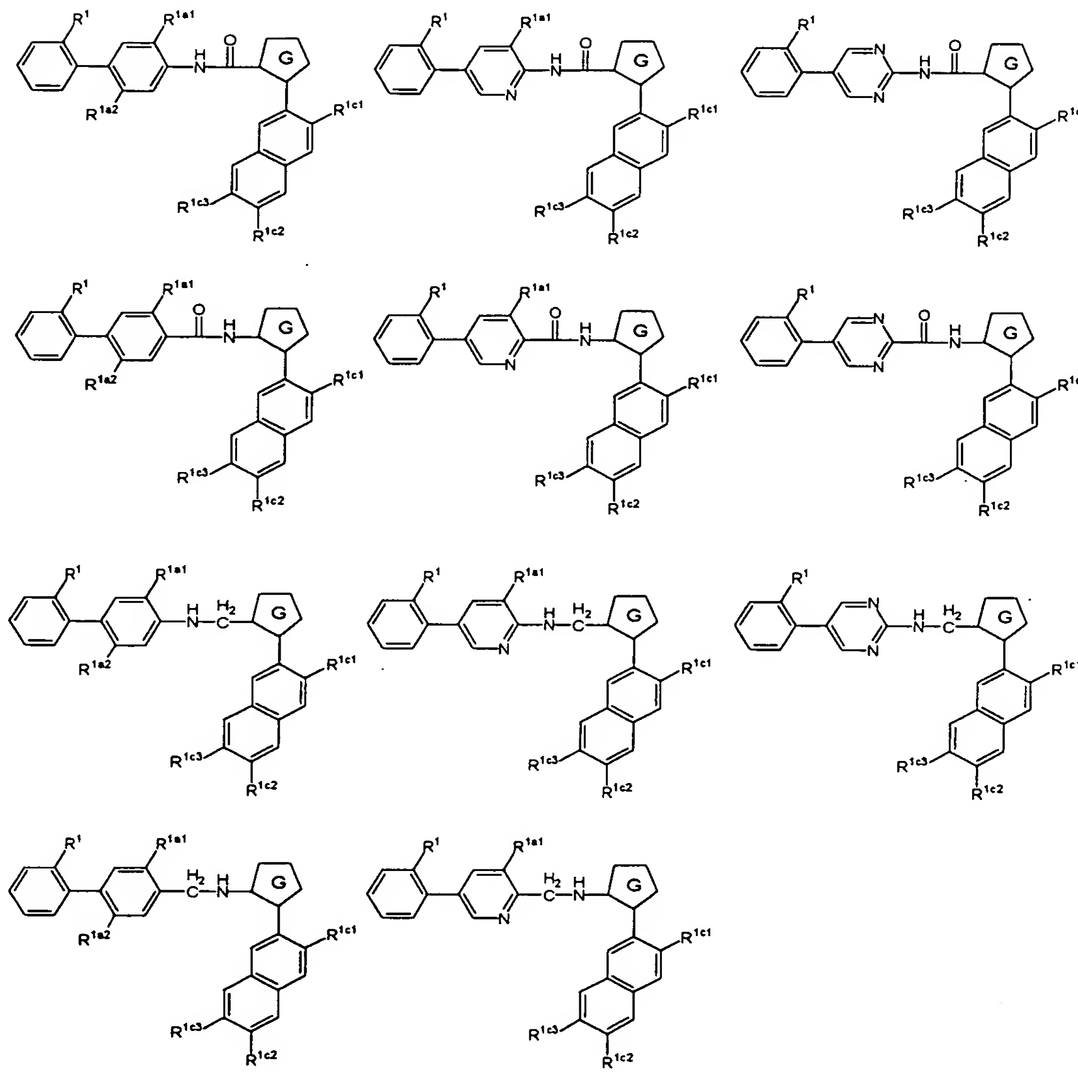
R^{1b} is selected from the group consisting of –H, –CH_3, -CF_3, -CH_2CH_3, -CF_2CF_3, -CH_2NH_2, -$CONH_2$, -SO_2CH_3, -SO_2NH_2, –NH_2COCH_3 and –NH_2COCF_3;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2.

Table 11



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

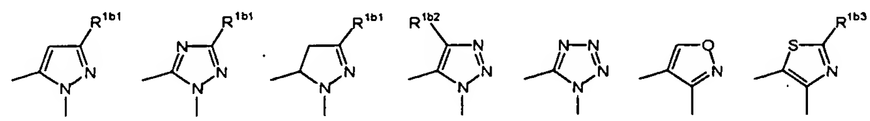
R^{1a1} and R^{1a2} are independently selected from group consisting of $-H$, $-F$, $-Cl$ and $-Br$;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, -CH_2OH, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

G is selected from the group consisting of:



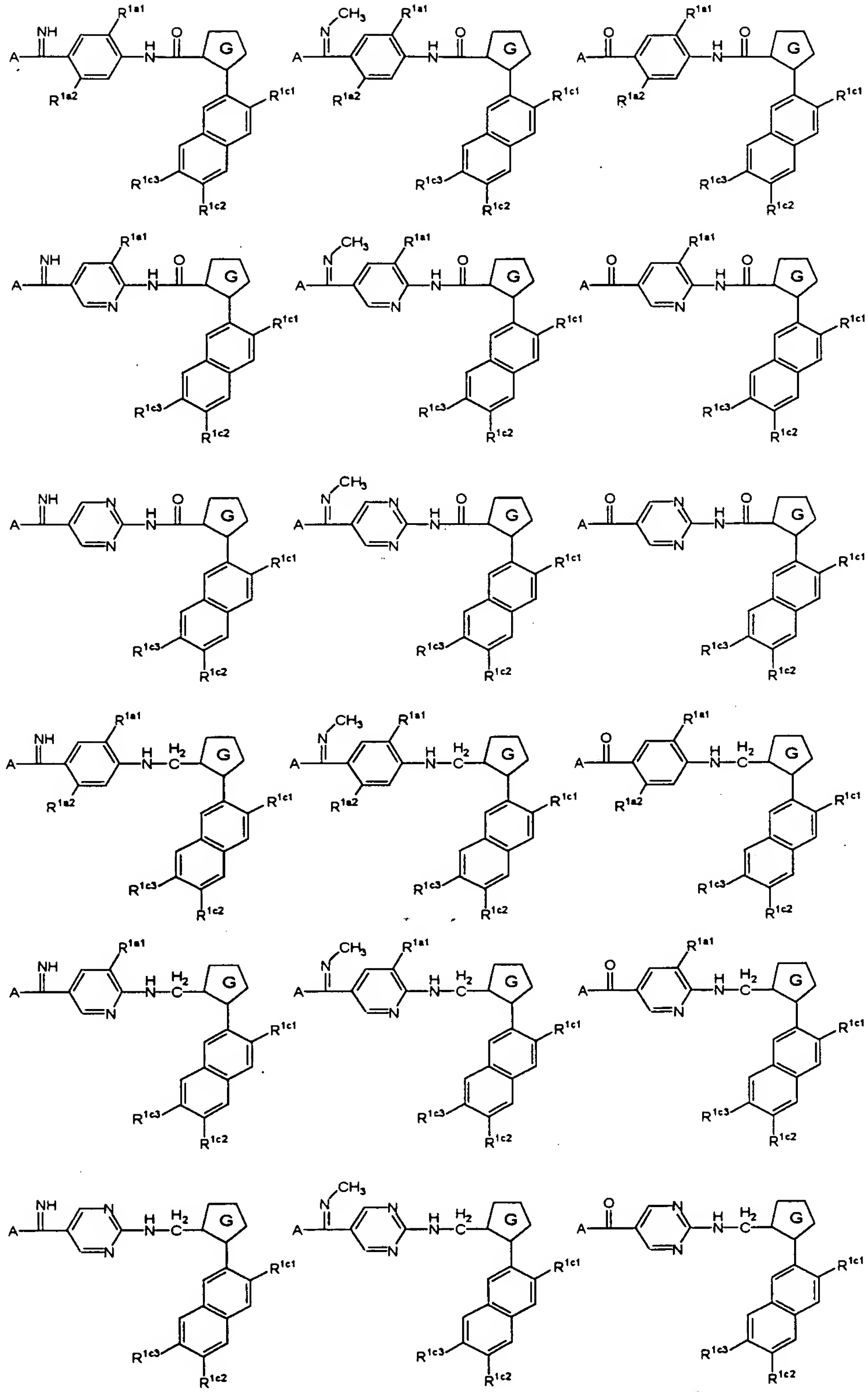
wherein:

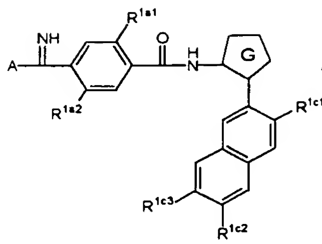
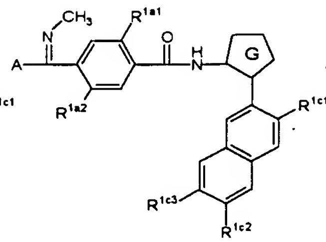
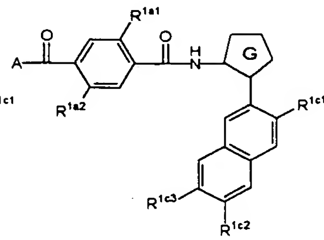
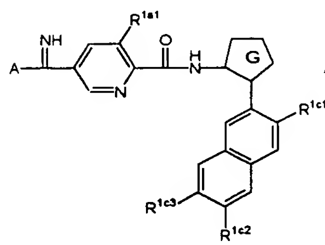
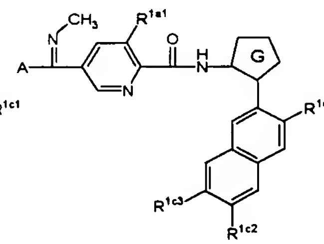
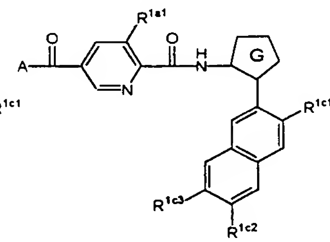
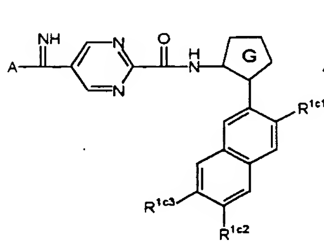
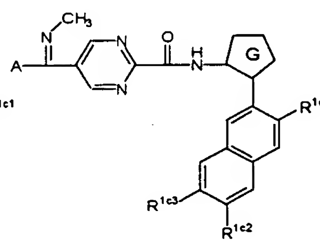
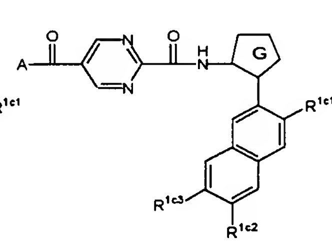
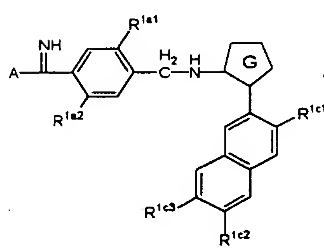
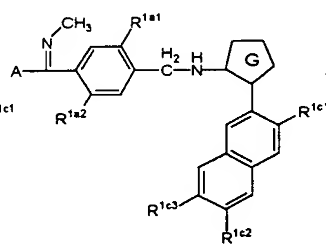
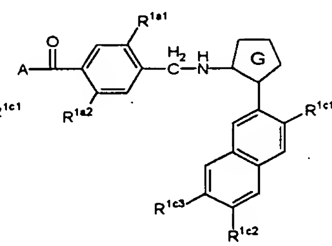
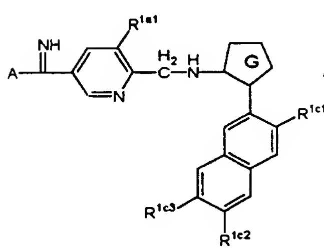
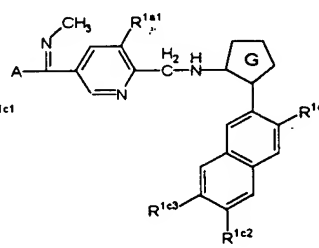
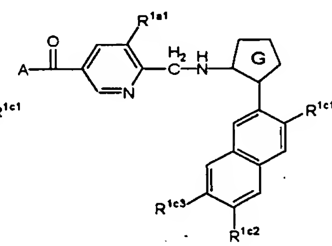
R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

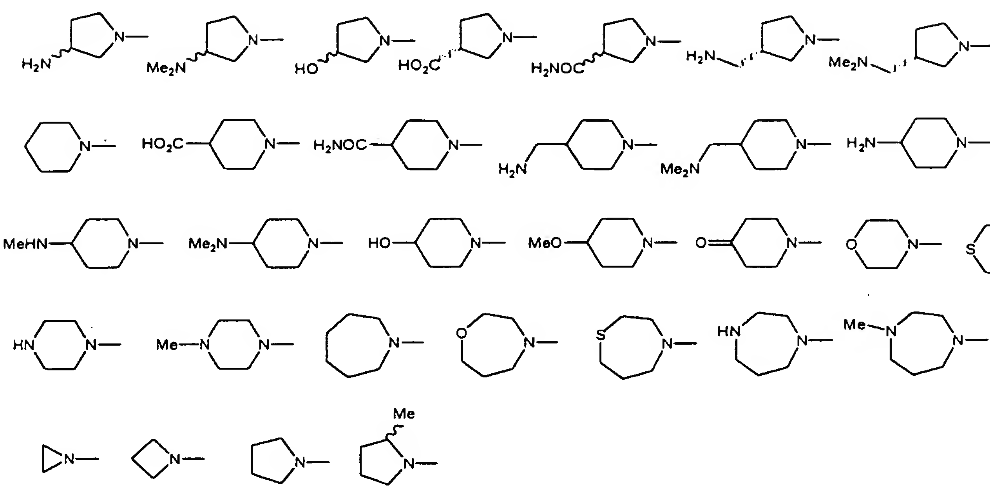
Table 12



wherein:

A is selected from the group consisting of:



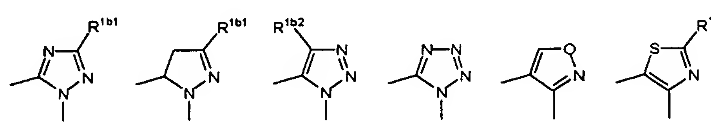
R^{1a1} and R^{1a2} are independently selected from the group consisting of –H, -F, -Cl and –Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

G is selected from the group consisting of:



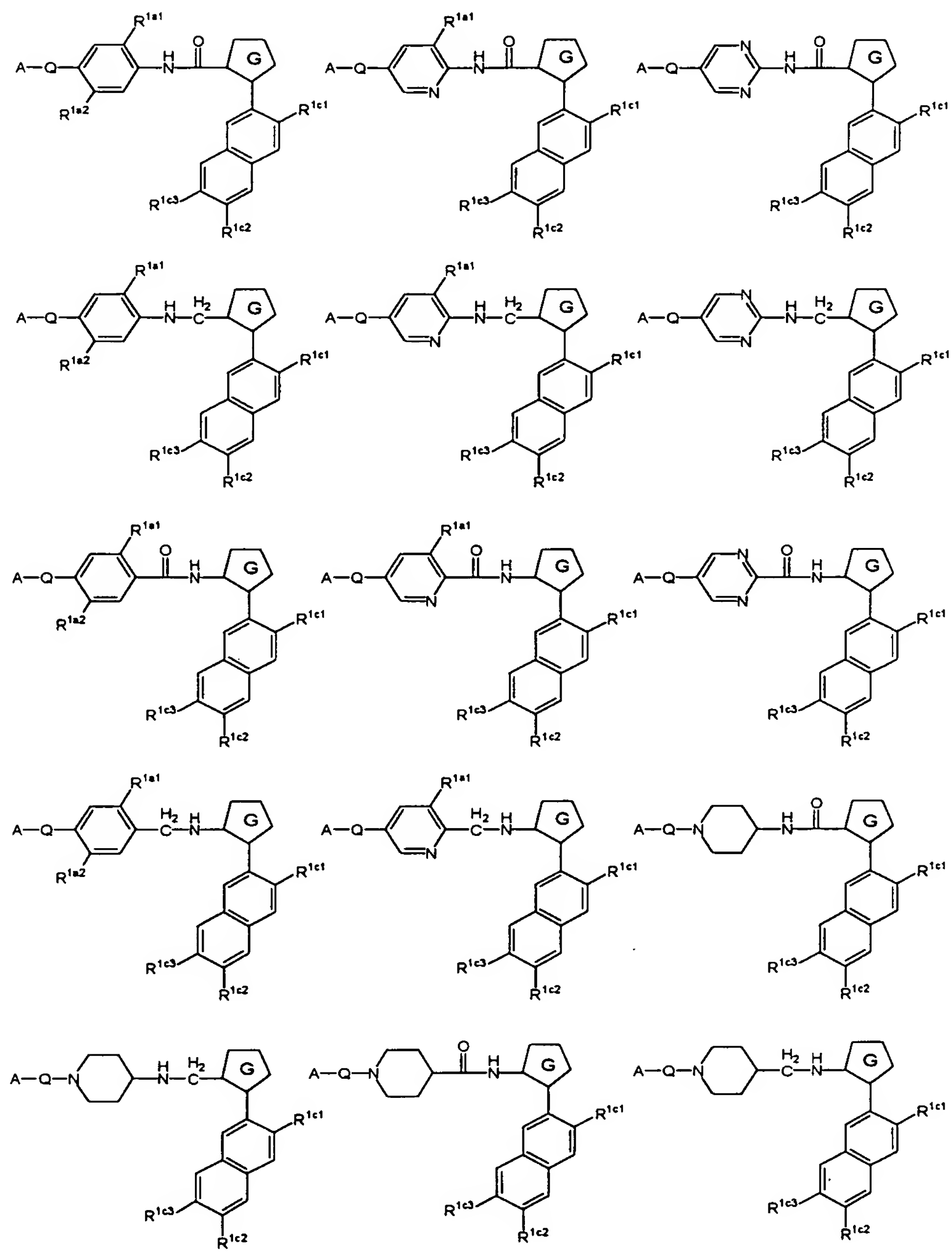
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

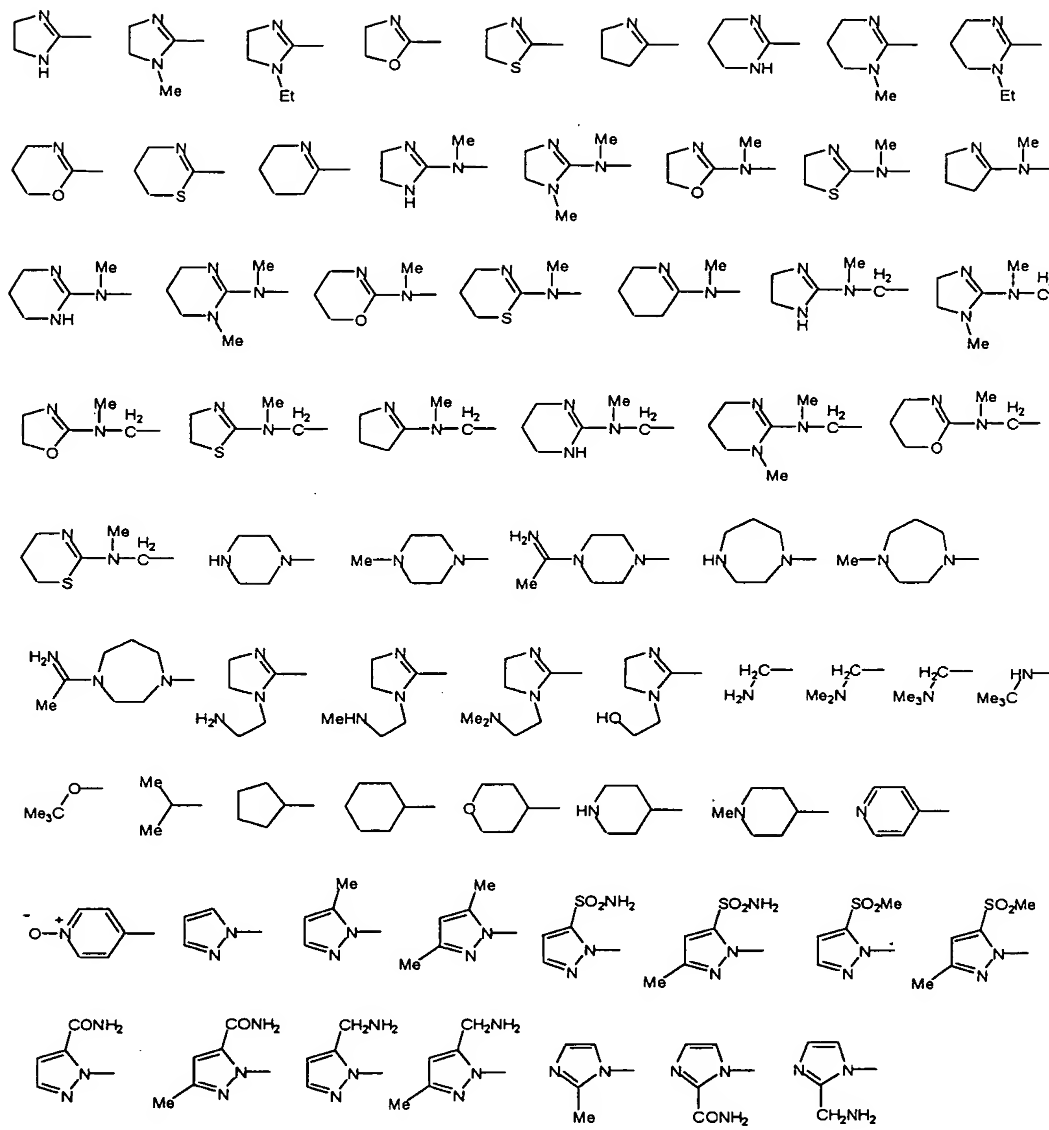
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 13



wherein:

A-Q is selected from the group consisting of:



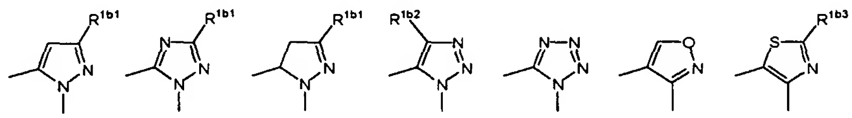
R^{1a1} and R^{1a2} are independently selected from the group consisting of –H, -F, -Cl and –Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

G is selected from the group consisting of:



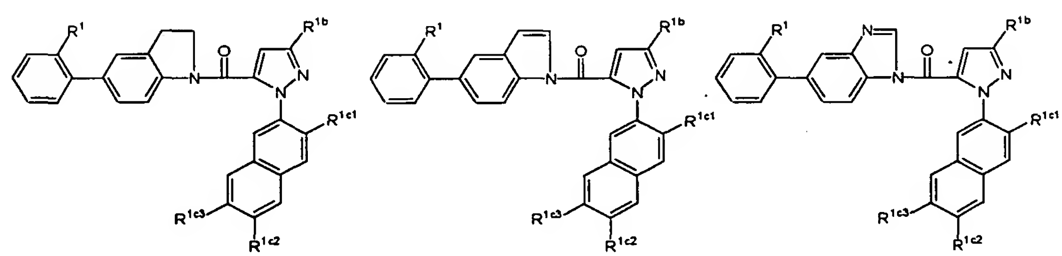
wherein:

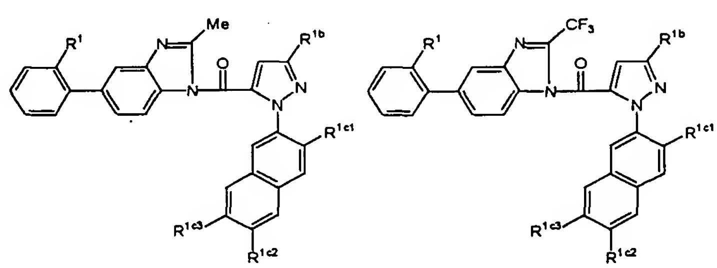
R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 14





wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

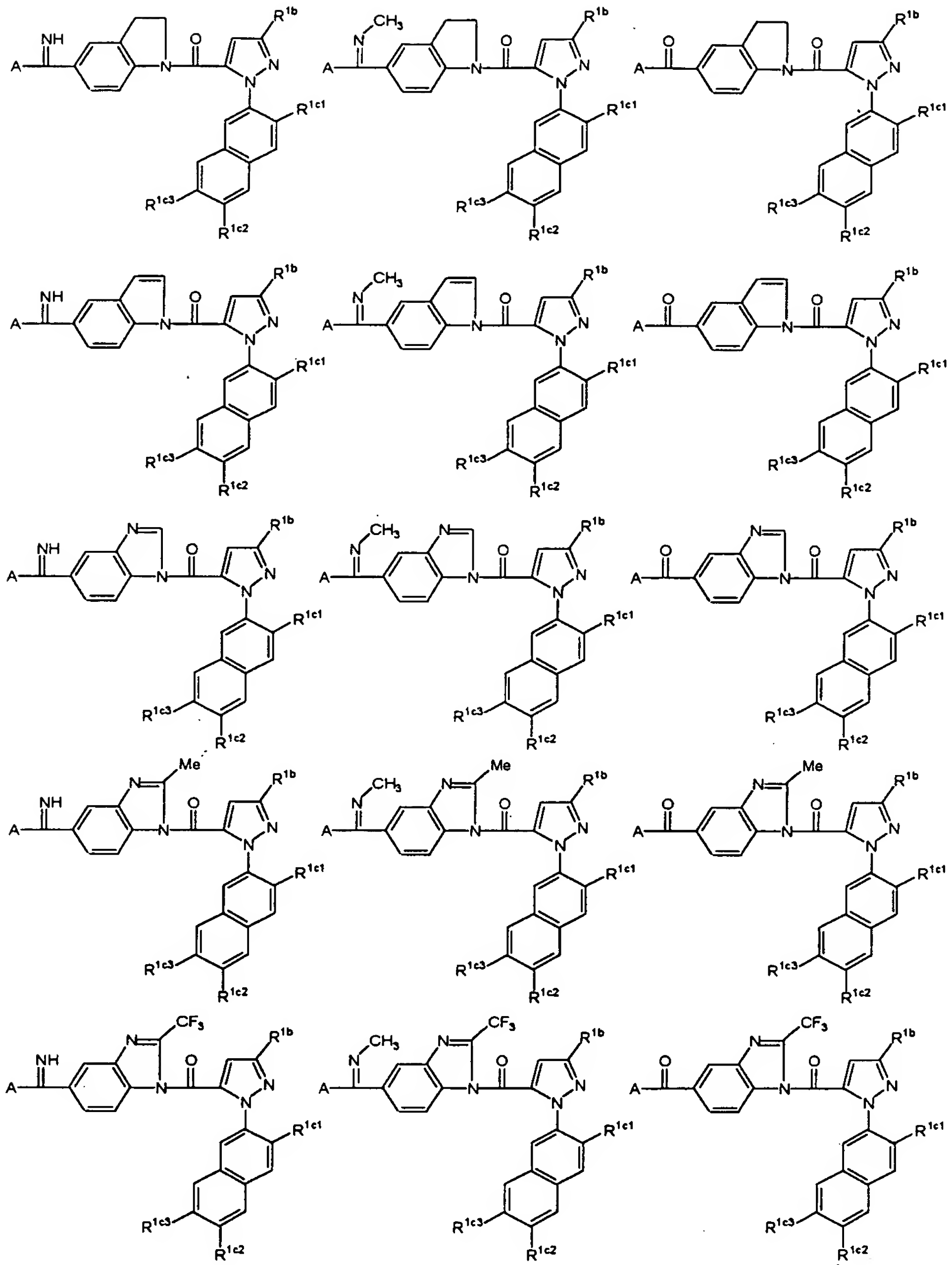
R^{1b} is selected from the group consisting of $-H$, $-CH_3$, $-CF_3$;

R^{1c1} is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, $-OH$, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$, $-OH$, $-OCH_3$, and $-NH_2$;

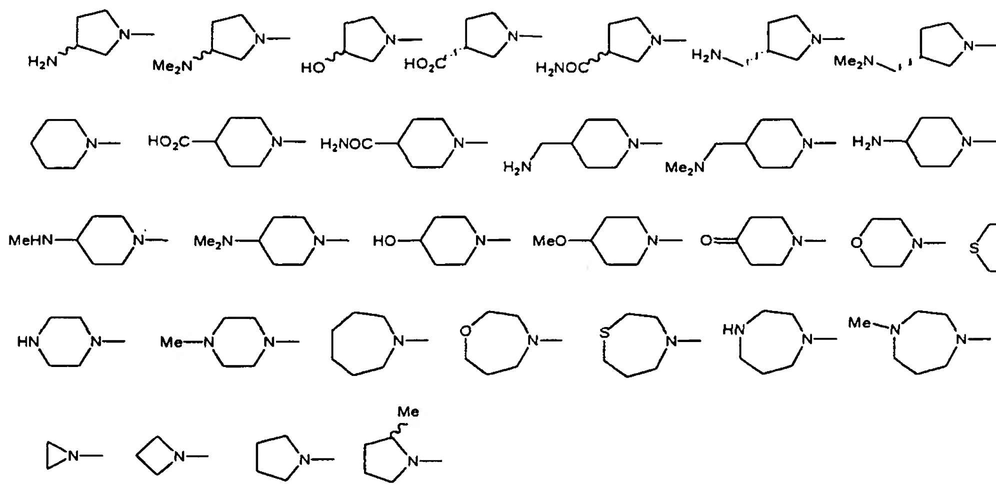
R^{1c3} is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$, $-OH$, $-OCH_3$, and $-NH_2$.

Table 15



wherein:

A is selected from the group consisting of:



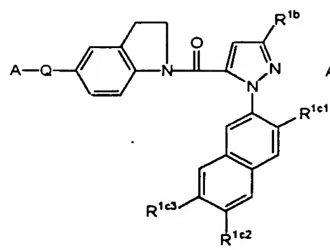
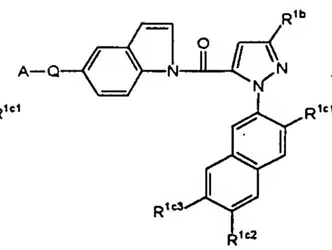
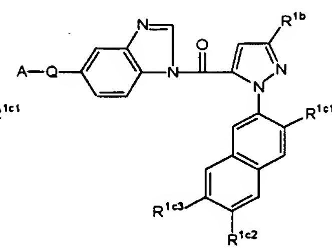
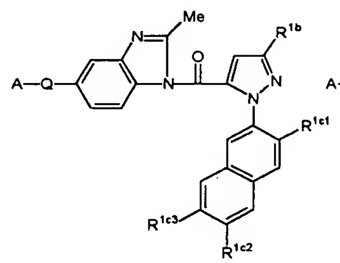
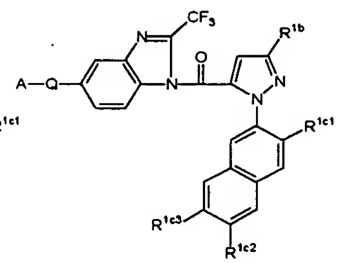
R^{1b} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

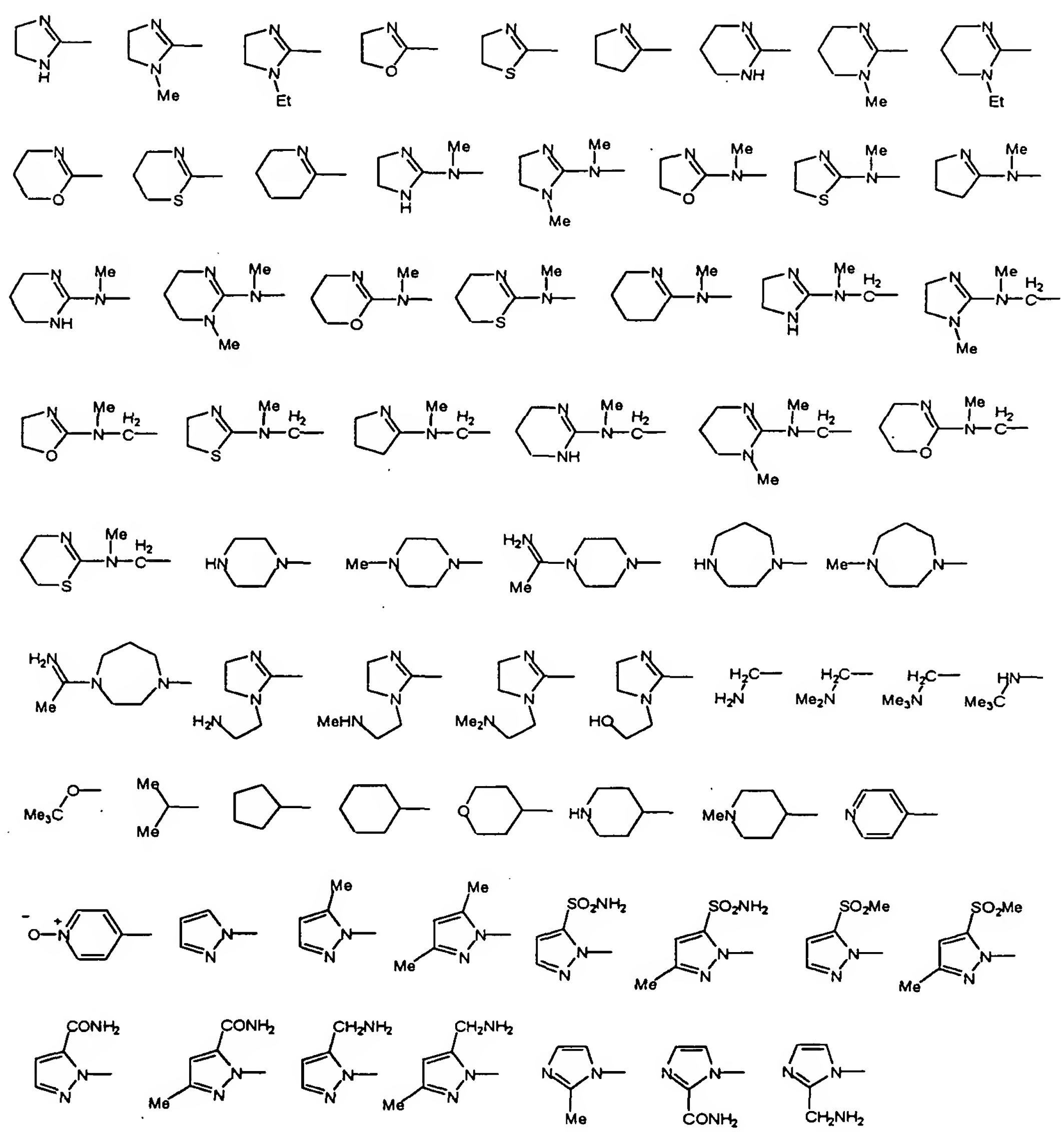
R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$.

Table 16

wherein:

A-Q is selected from the group consisting of:



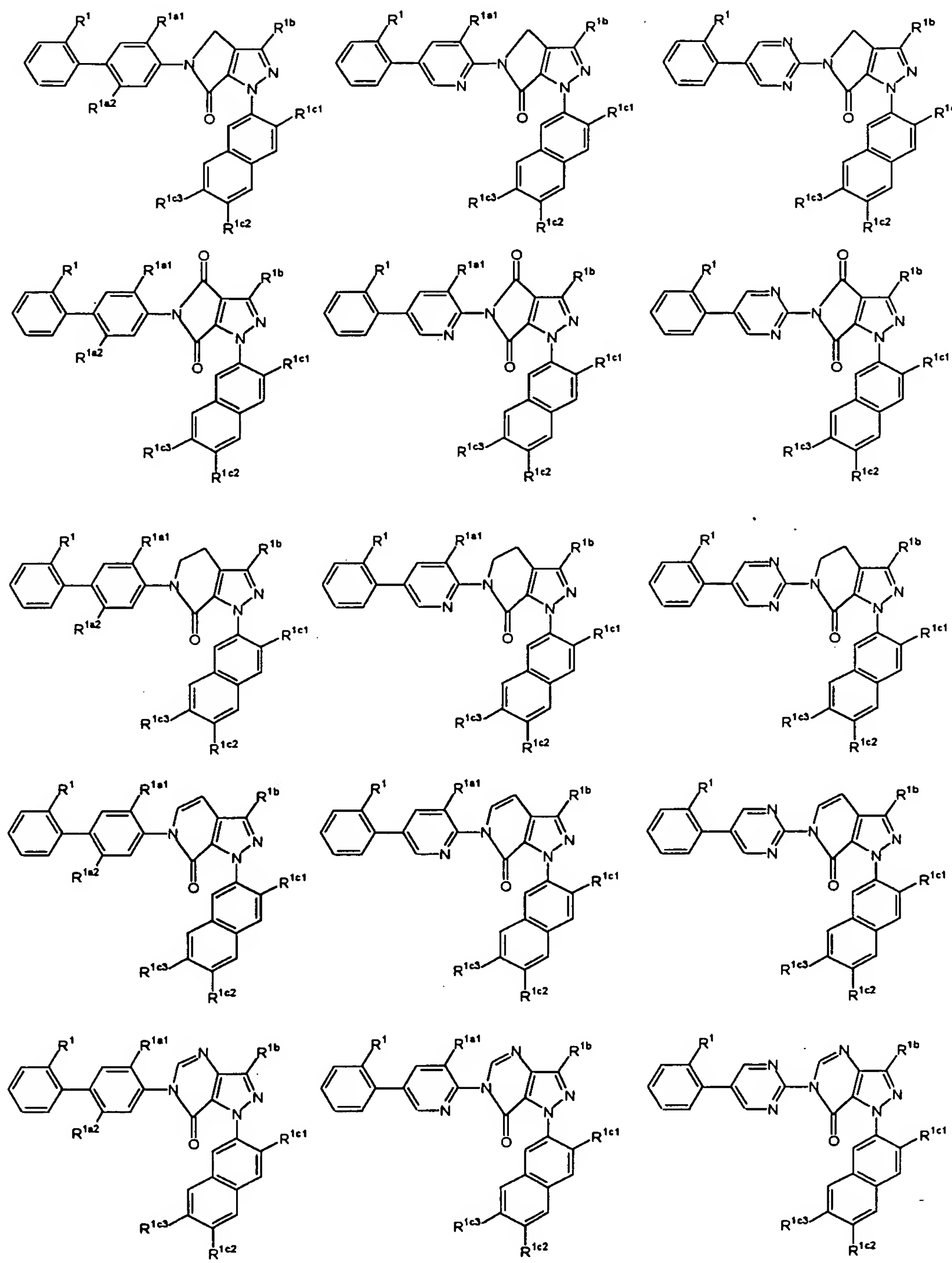
R^{1b} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

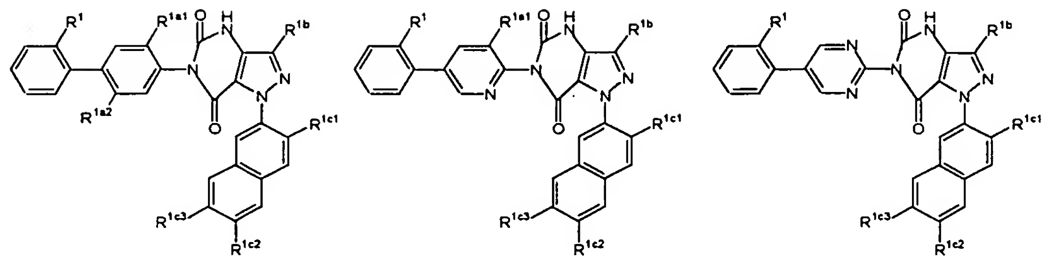
R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$.

Table 17





wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a1} and R^{1a2} are independently selected from the group consisting of $-H$, $-F$, $-Cl$ and Br;

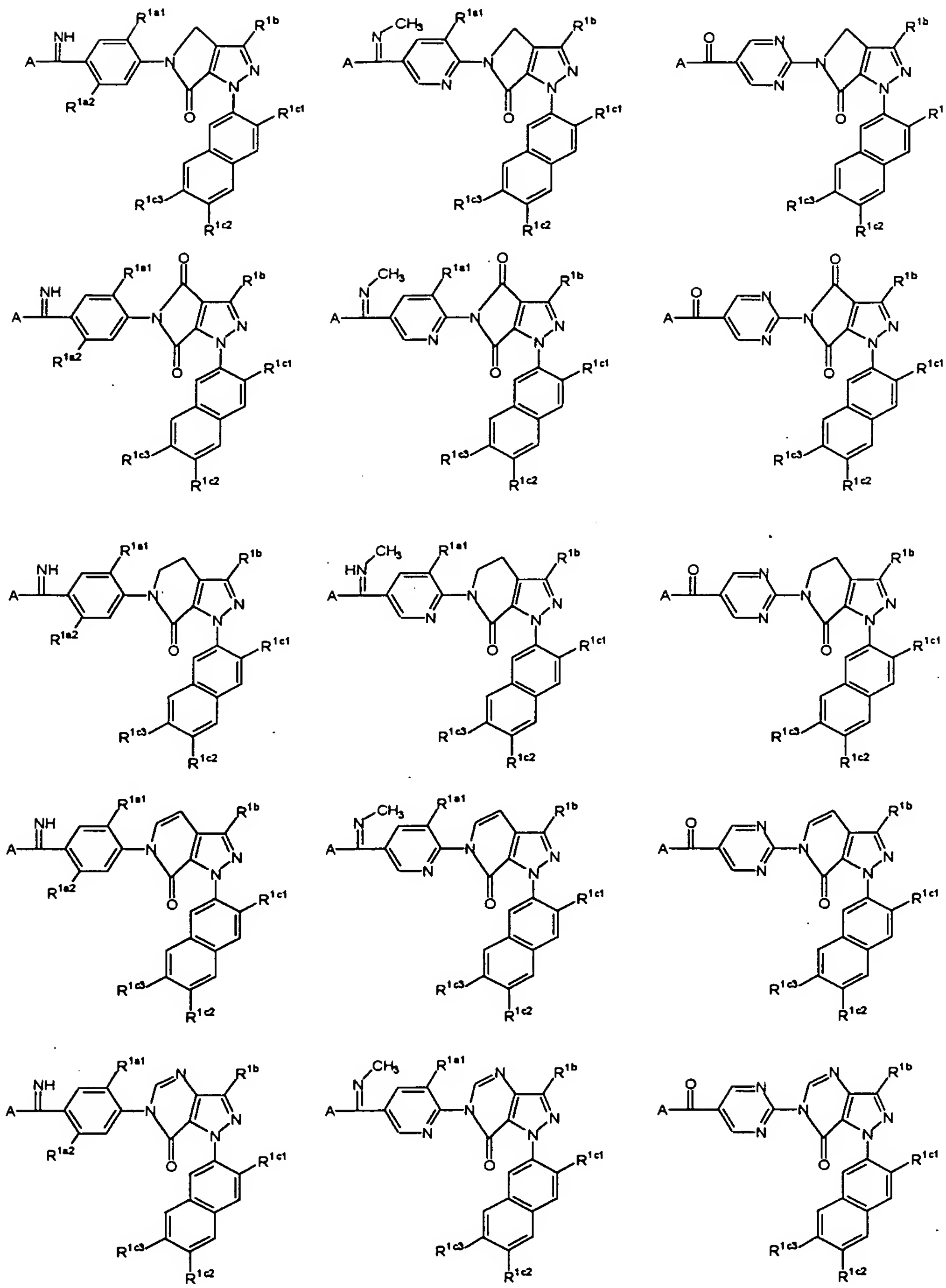
R^{1b} is selected from the group consisting of $-H$, $-CH_3$ and $-CF_3$;

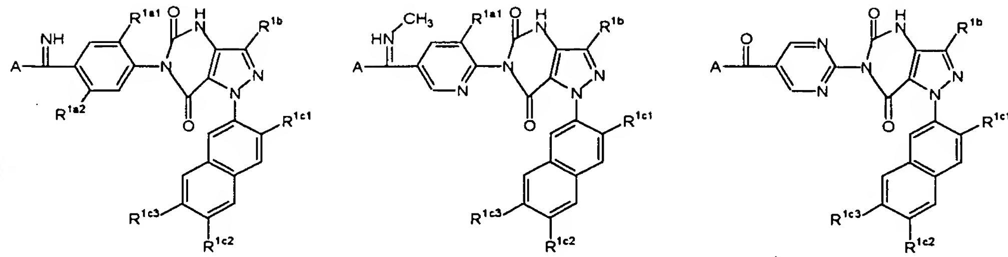
R^{1c1} is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, $-OH$, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$, $-OH$, $-OCH_3$, and $-NH_2$;

R^{1c3} is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$, $-OH$, $-OCH_3$, and $-NH_2$.

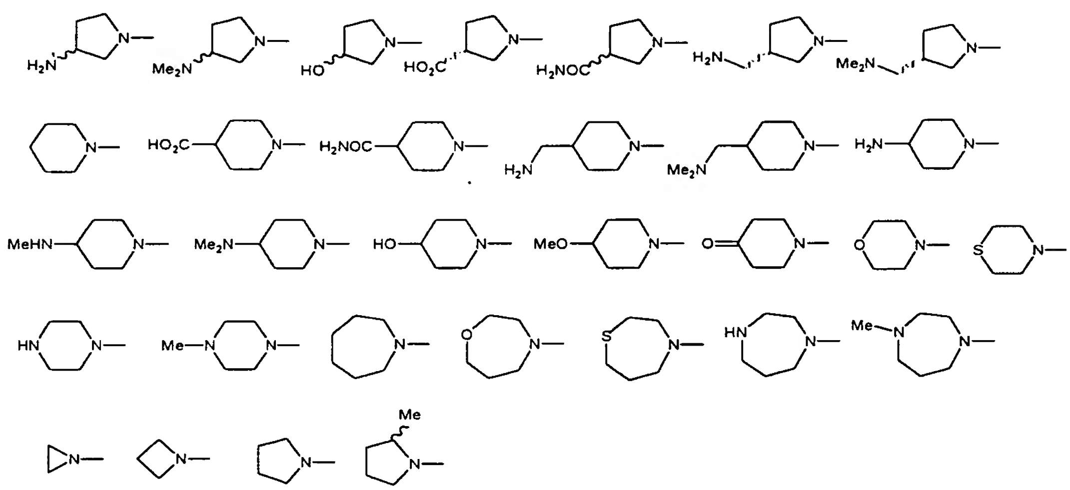
Table 18





wherein:

A is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of –H, -F, -Cl and Br;

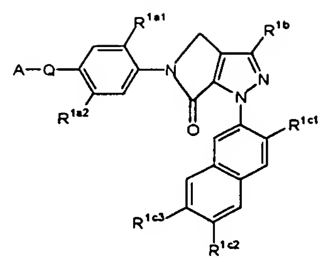
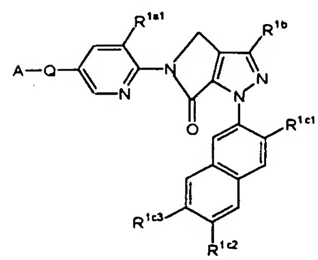
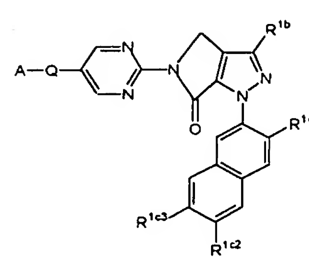
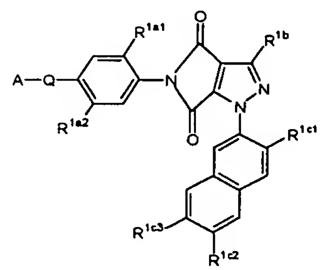
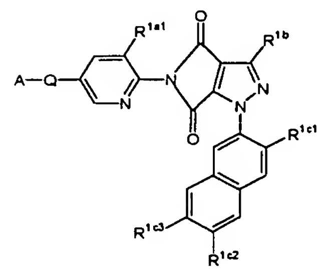
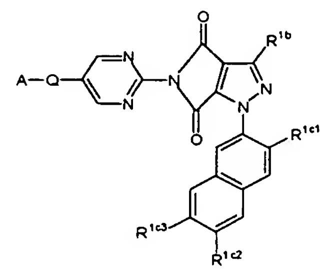
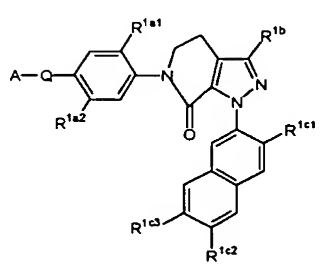
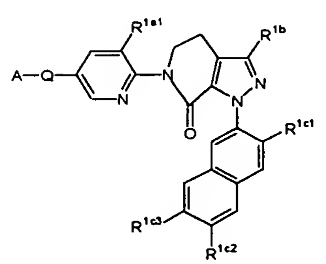
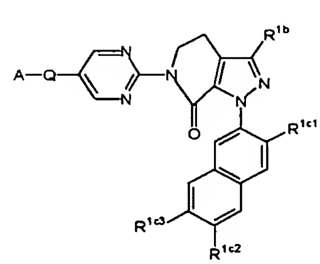
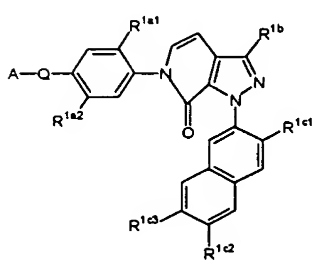
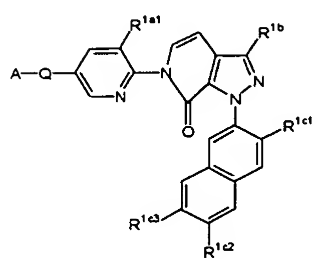
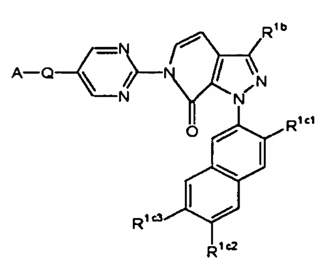
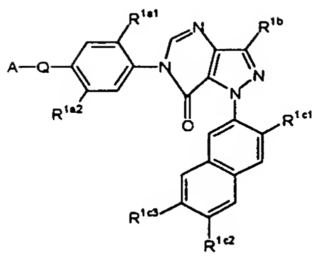
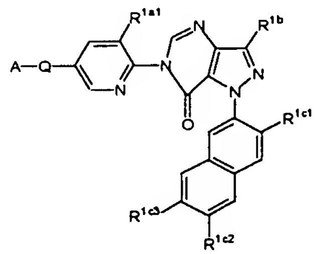
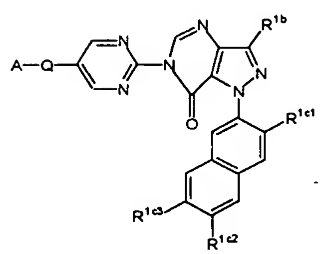
R^{1b} is selected from the group consisting of –H, –CH_3 and -CF_3;

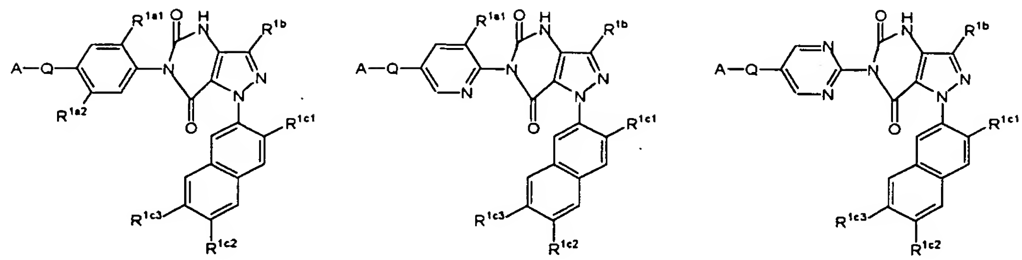
R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, -OCH_3, and –NH_2.

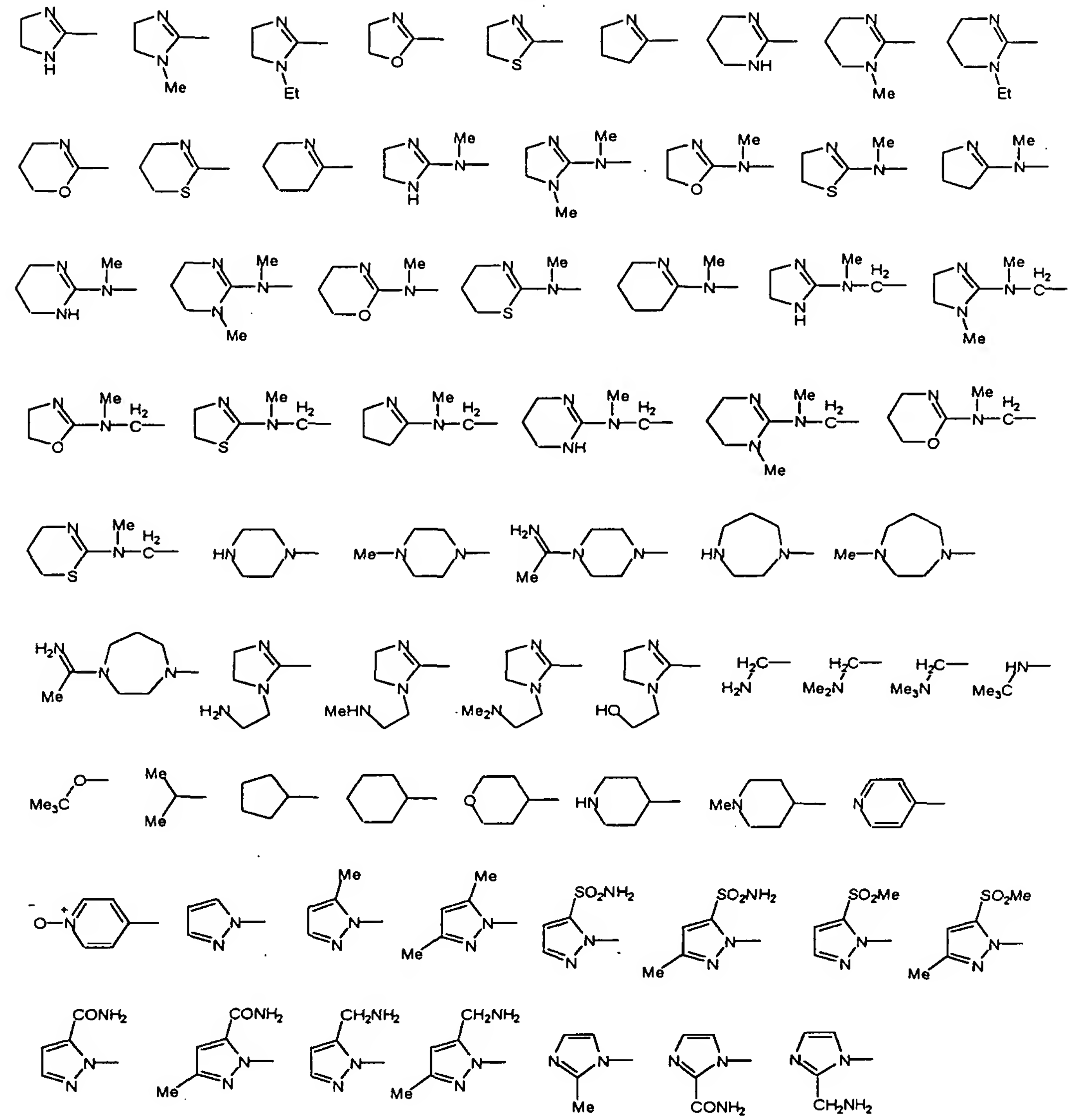
Table 19



wherein:

A-Q is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of –H, -F, -Cl and Br;

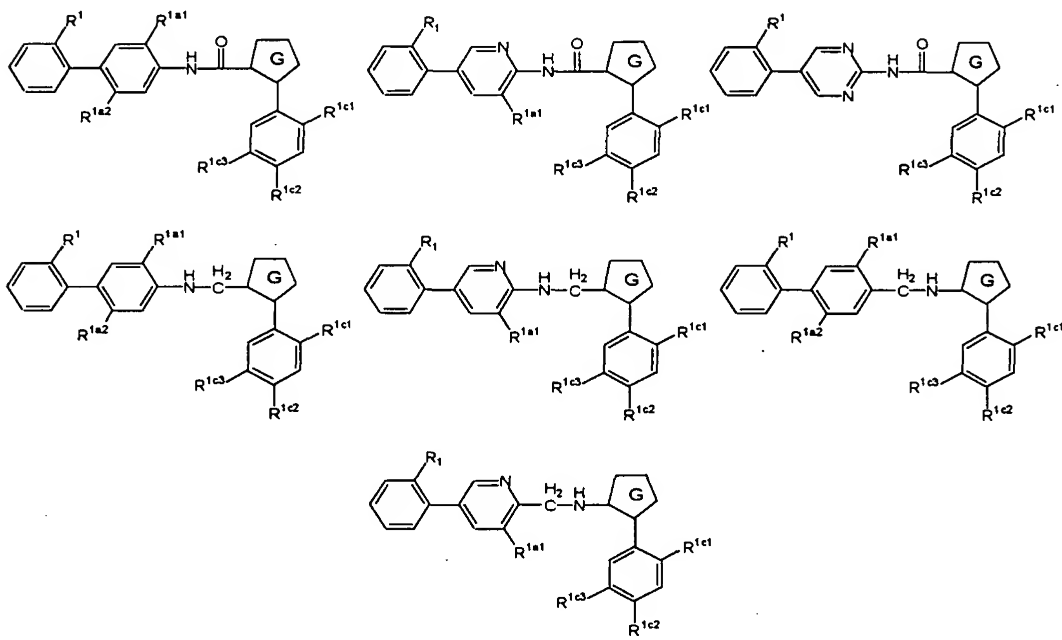
R^{1b} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $-NH_2$.

Table 20



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, –CN, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

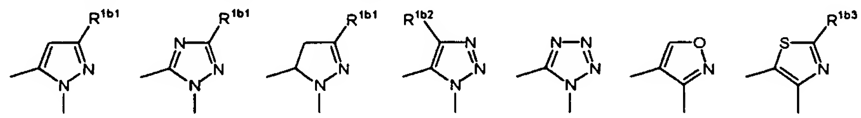
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, $-NH_2$, $-CONH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=NH)NH_2$;

G is selected from the group consisting of:



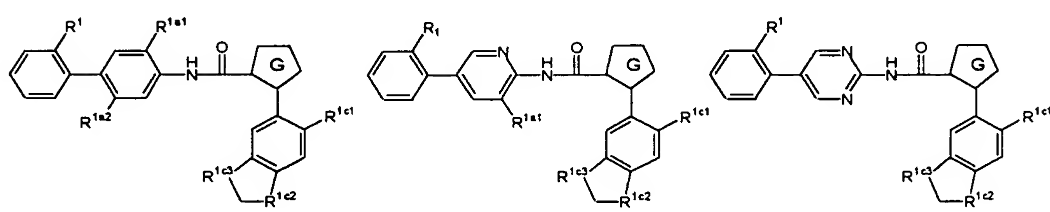
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 21



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, –CN, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

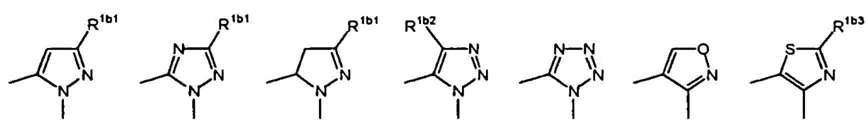
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of $-CH_2-$, -O-, -NH-, $-N(CH_3)-$, $-CH_2CH_2-$, $-O-CH_2-$, $-NH-CH_2-$, and $-N(CH_3)-CH_2-$;

R^{1c3} is selected from the group consisting of $-CH_2-$, -O-, -NH-, $-N(CH_3)-$, and $-CH(NH_2)-$;

G is selected from the group consisting of:



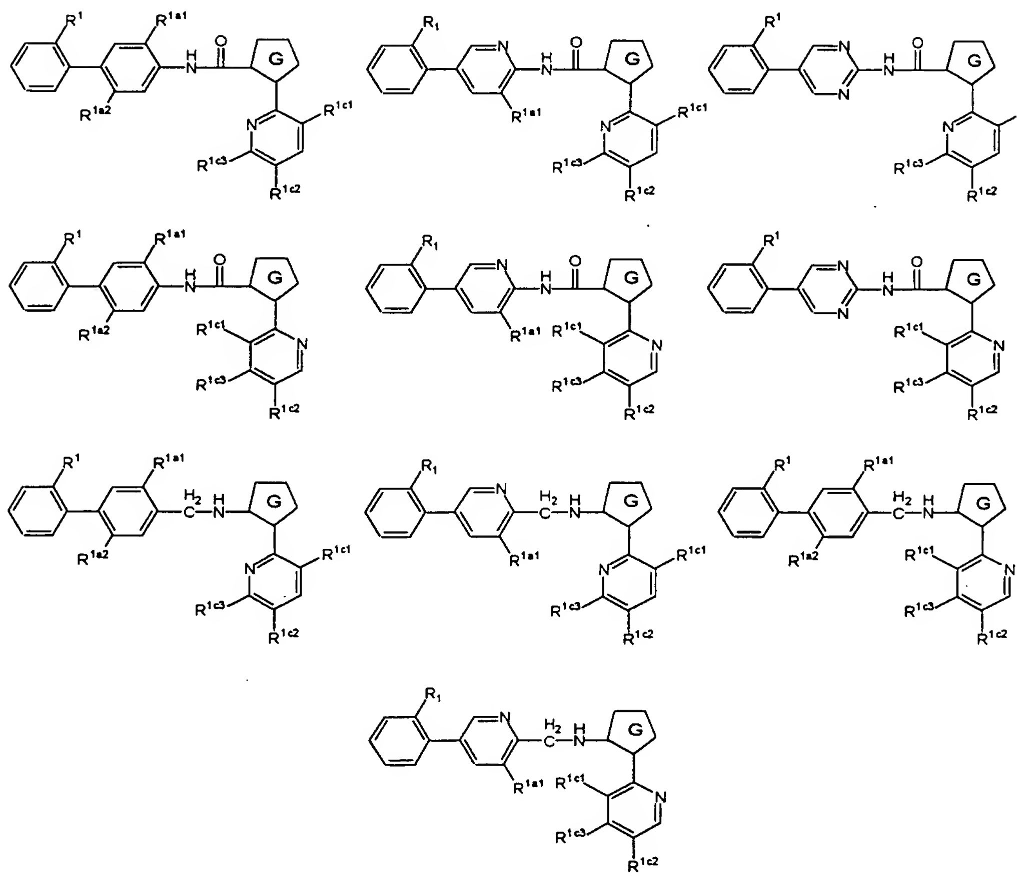
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 22



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, –CN, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

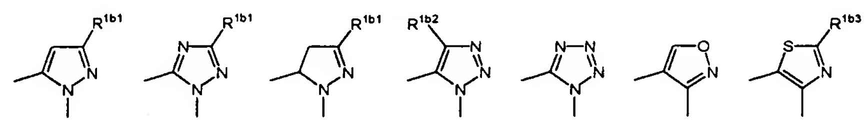
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, $-NH_2$, $-CONH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=NH)NH_2$;

G is selected from the group consisting of:



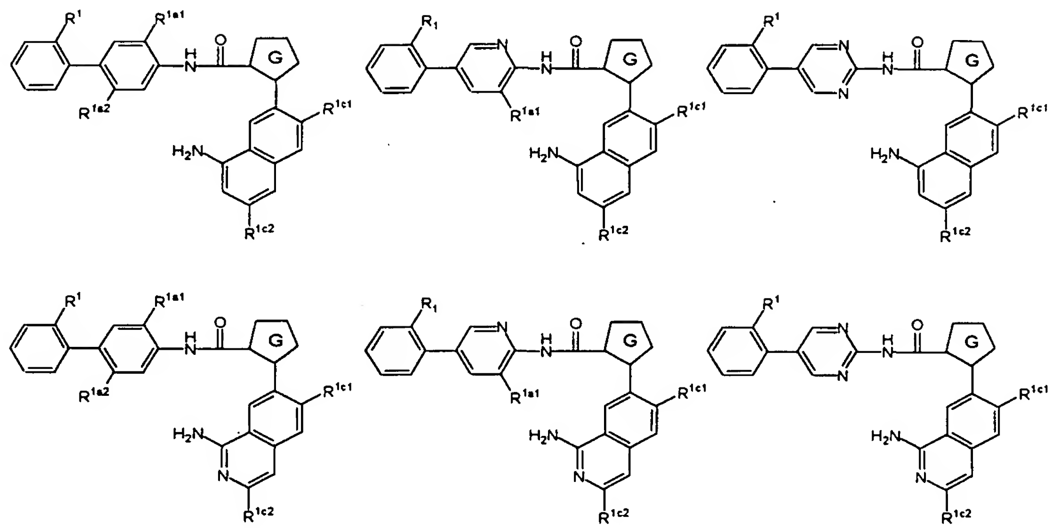
Wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 23



wherein:

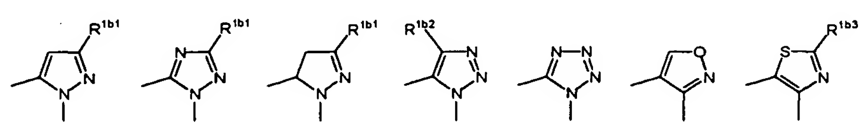
R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



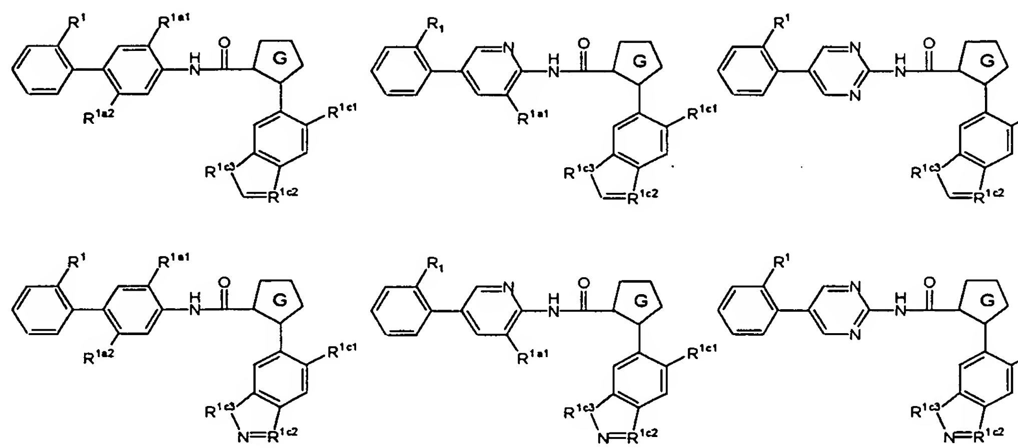
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

Table 24



wherein:

R^1 is selected from the group consisting of -SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

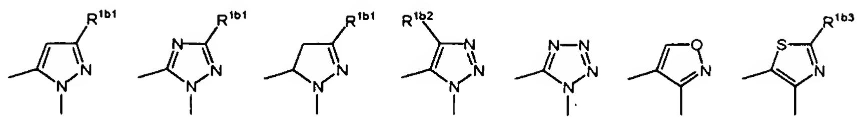
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –CH-, and –N-;

R^{1c3} is selected from the group consisting of –NH-, and –O-;

G is selected from the group consisting of:



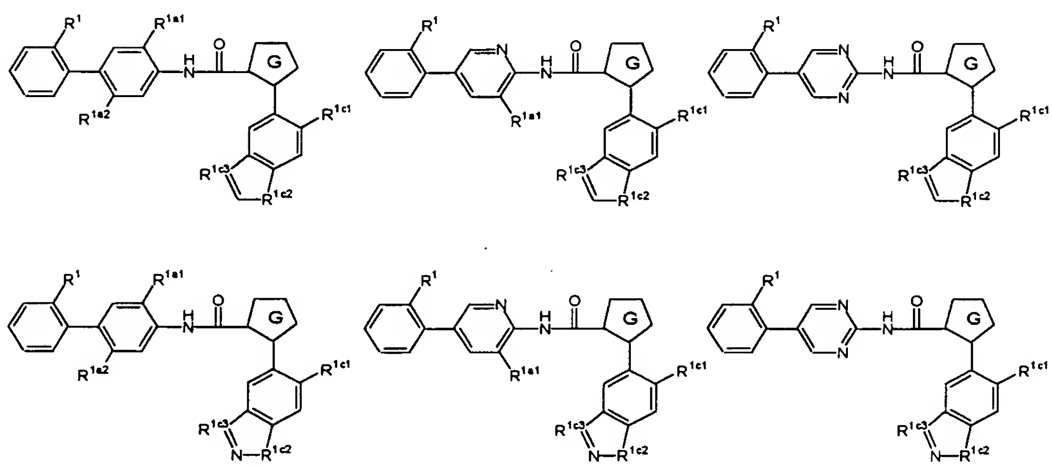
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

Table 25



wherein:

R^1 is selected from the group consisting of -SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

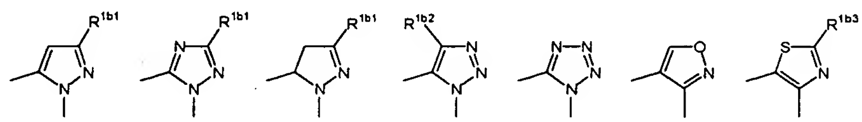
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of $-CH_2$-, -O- and –NH-;

R^{1c3} is selected from the group consisting of –CH-, $-C(NH_2)$- and –N-;

G is selected from the group consisting of:



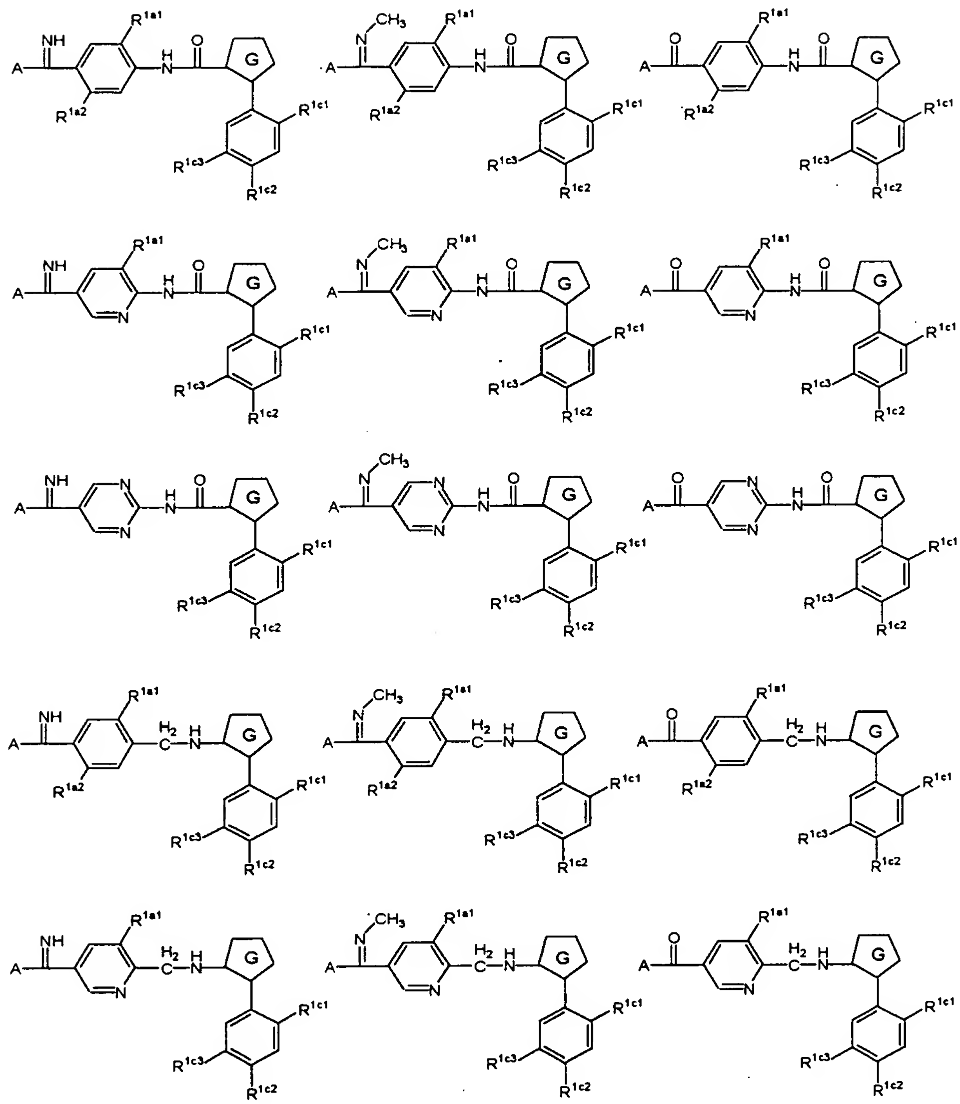
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

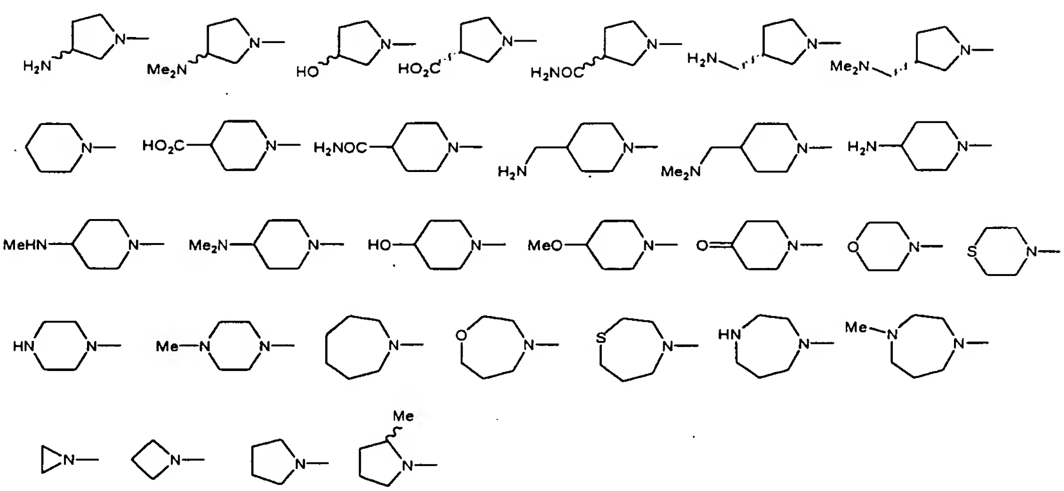
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 26



wherein:

A is selected from the group consisting of:



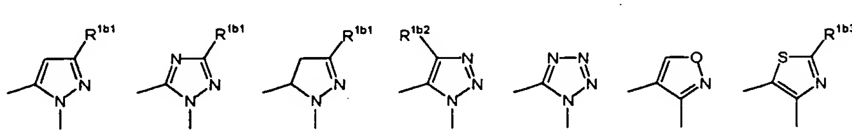
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, $–NH_2$, $-CONH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=NH)NH_2$;

G is selected from the group consisting of:



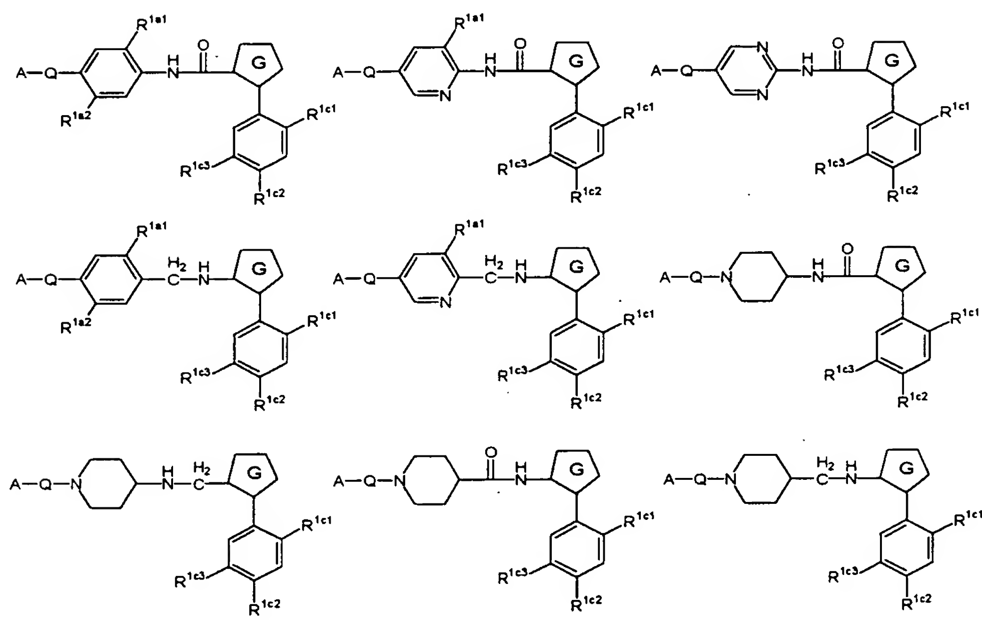
wherein:

R^{1b1} is selected from the group consisting of $-H$, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of $-H$, $-CH_3$ and $-CF_3$;

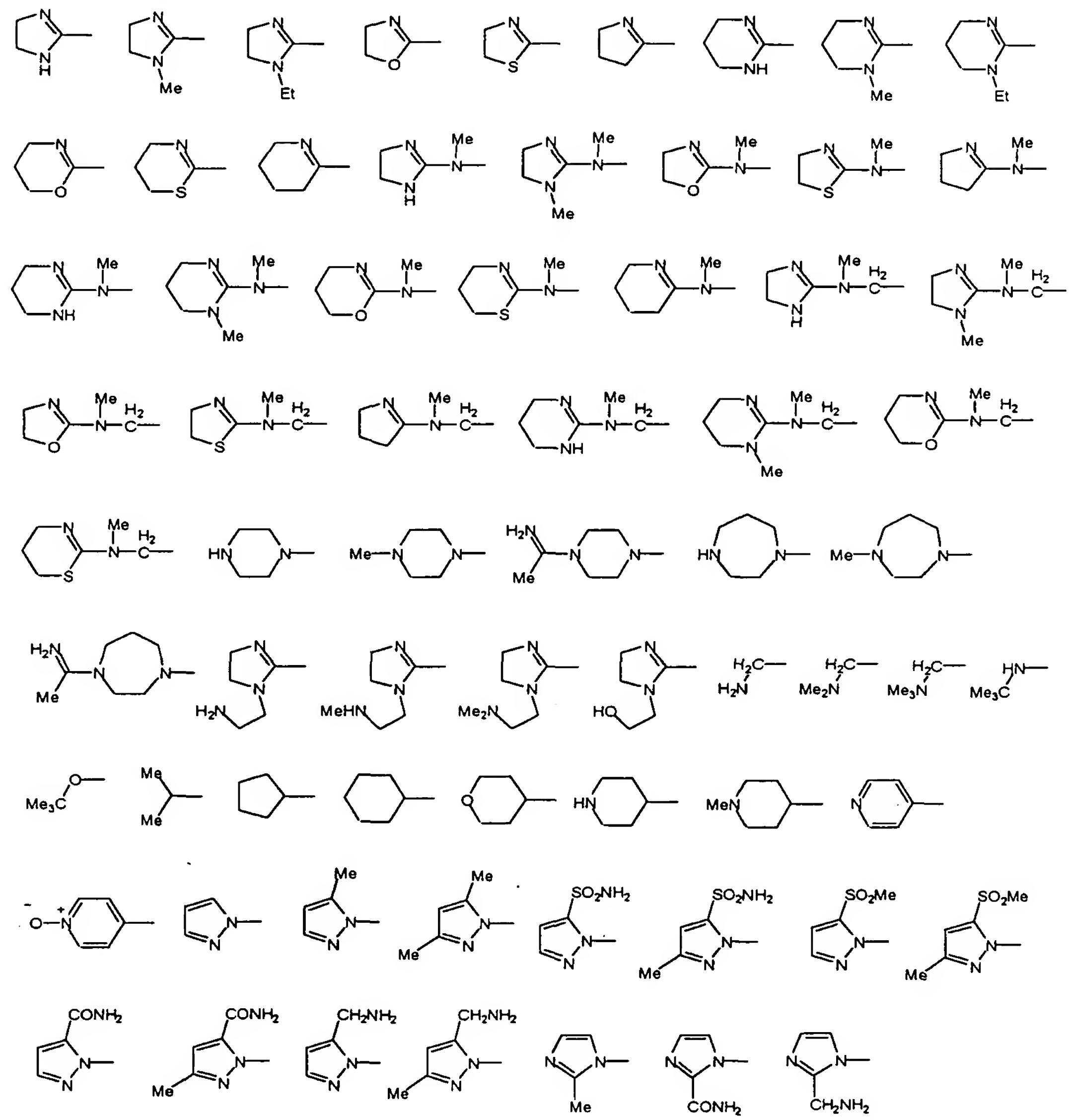
R^{1b3} is selected from the group consisting of $-Cl$, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 27



wherein:

A-Q is selected from the group consisting of:



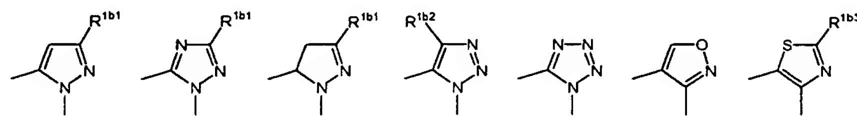
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, $-NH_2$, $-CONH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=NH)NH_2$;

G is selected from the group consisting of:



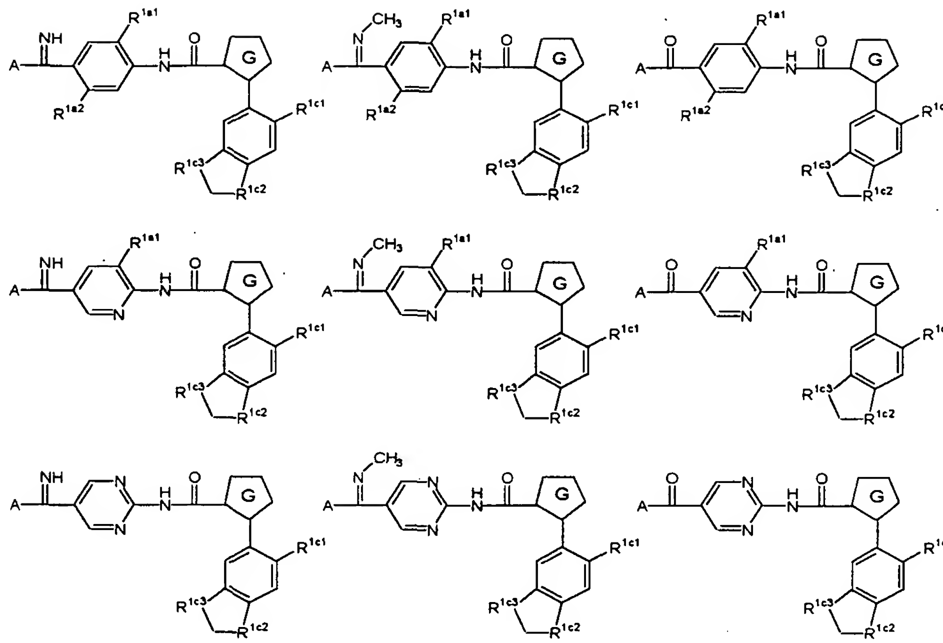
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

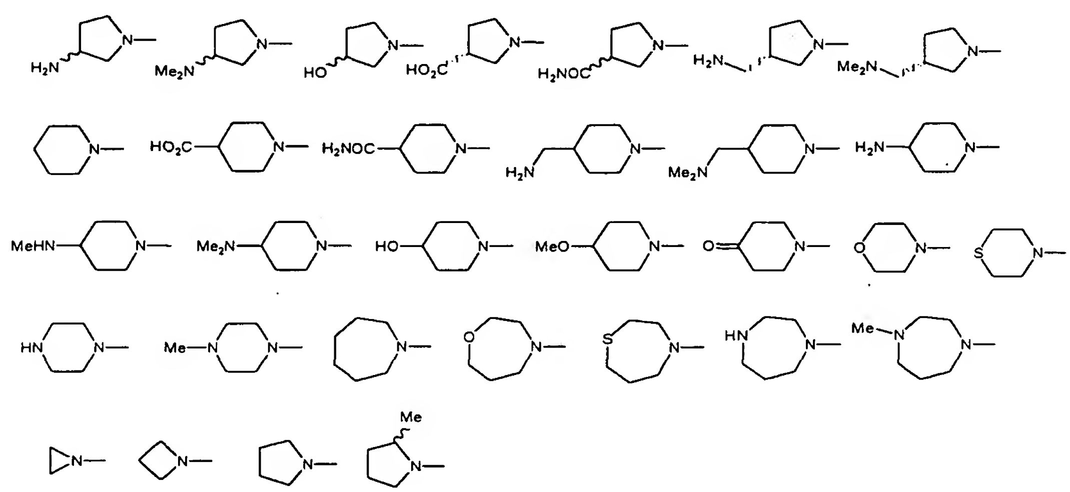
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 28



wherein:

A is selected from the group consisting of:



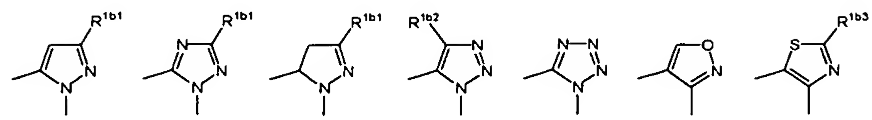
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, $-NH_2$, $-CONH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=NH)NH_2$;

G is selected from the group consisting of:



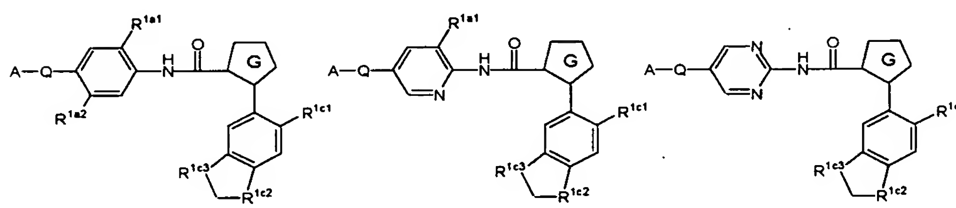
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

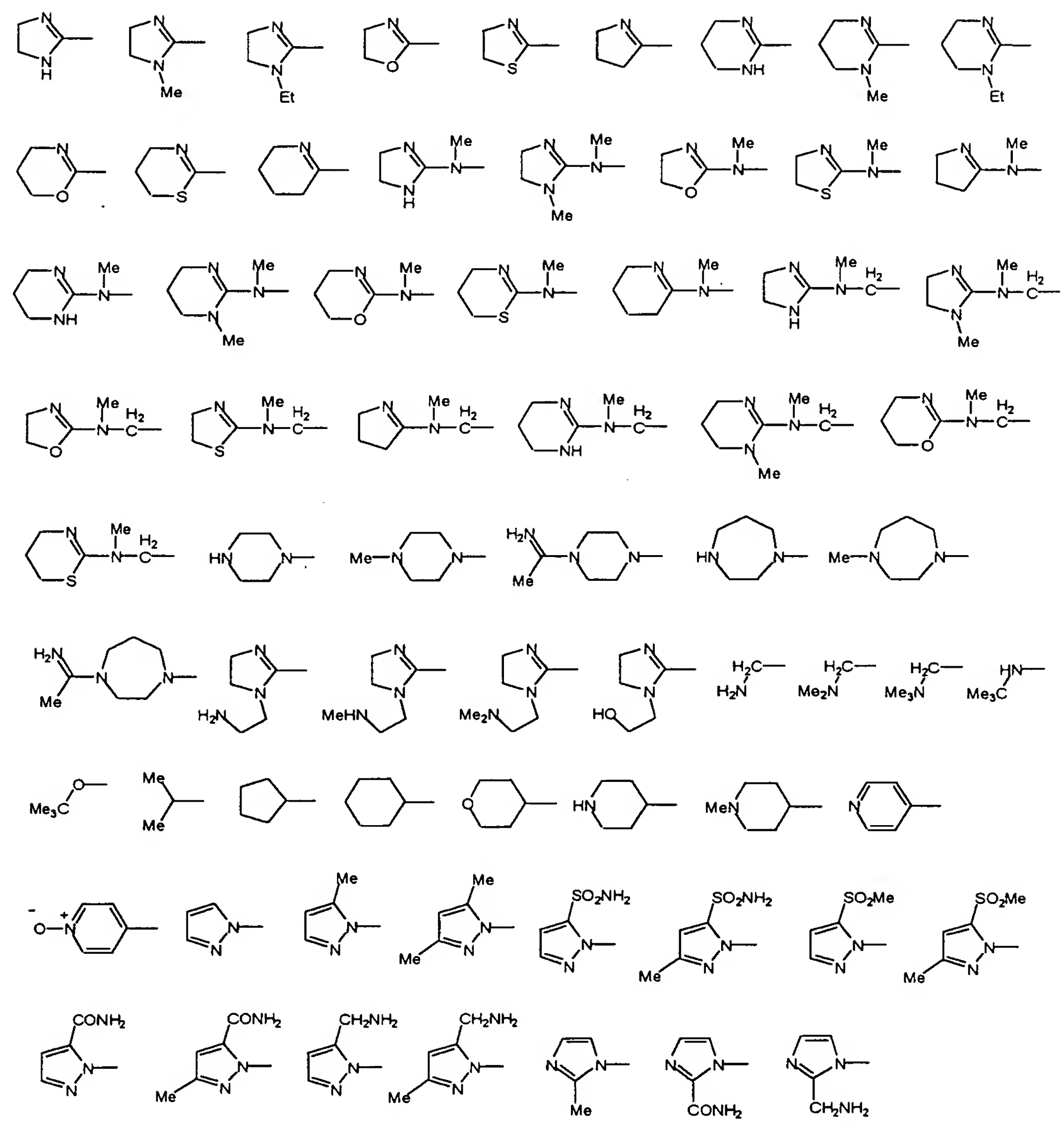
R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

Table 29



wherein:

A-Q is selected from the group consisting of:



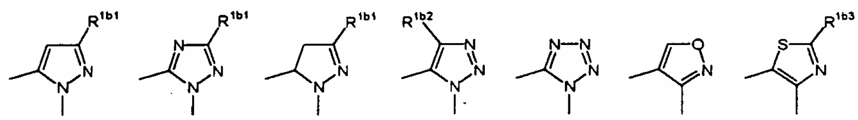
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of $-CH_2-$, -O-, -NH-, $-N(CH_3)-$, $-CH_2CH_2-$, $-O-CH_2-$, $-NH-CH_2-$, and $-N(CH_3)-CH_2-$;

R^{1c3} is selected from the group consisting of $-CH_2-$, -O-, -NH-, $-N(CH_3)-$, and $-CH(NH_2)-$.

G is selected from the group consisting of:



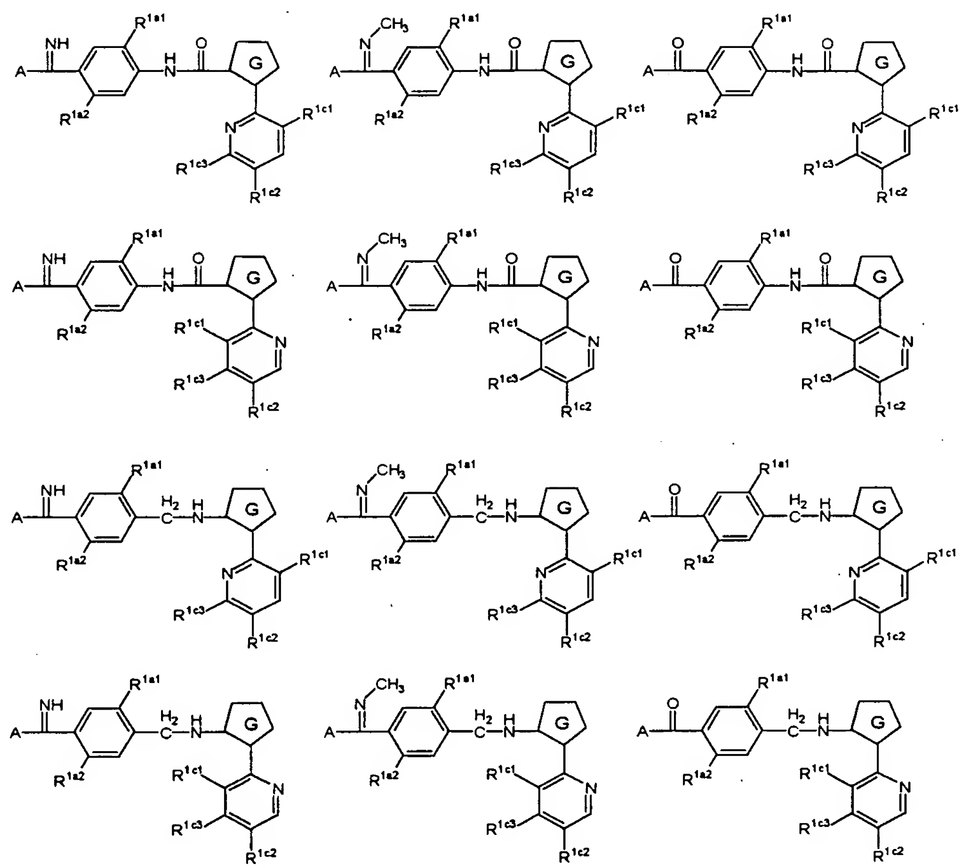
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

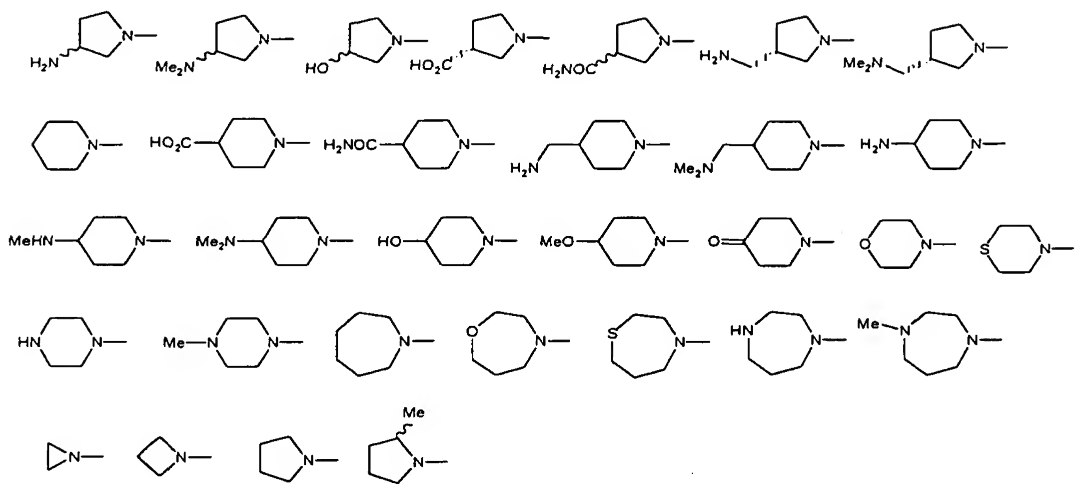
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 30



wherein:

A is selected from the group consisting of:



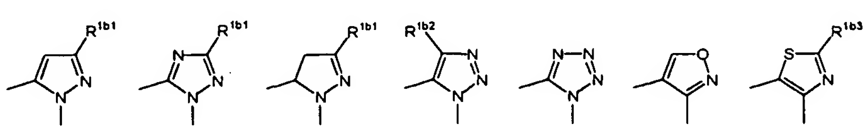
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, $–NH_2$, $-CONH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=NH)NH_2$, $-C(=NH)NH(CH_3)$, $-C(=NH)NH(CH_3)_2$;

G is selected from the group consisting of:



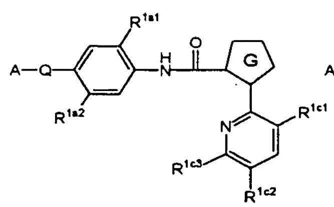
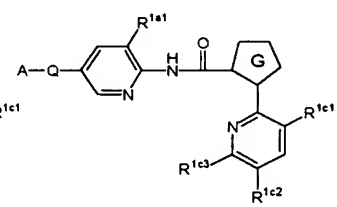
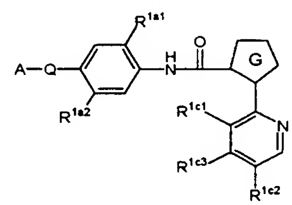
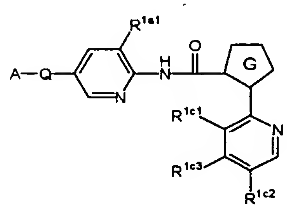
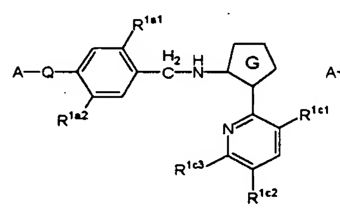
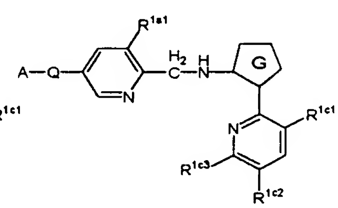
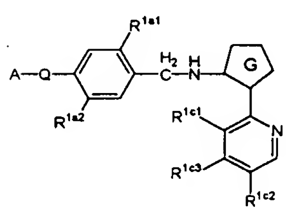
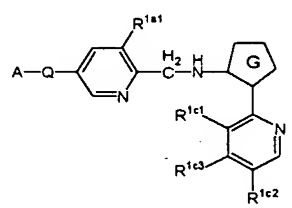
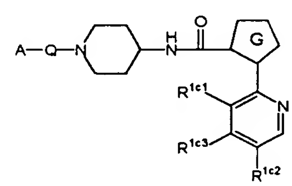
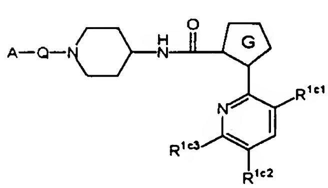
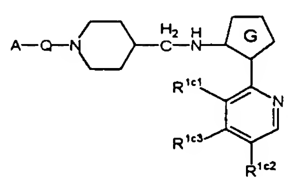
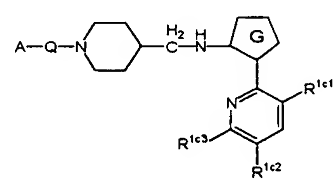
wherein:

R^{1b1} is selected from the group consisting of $-H$, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of $-H$, $-CH_3$ and $-CF_3$;

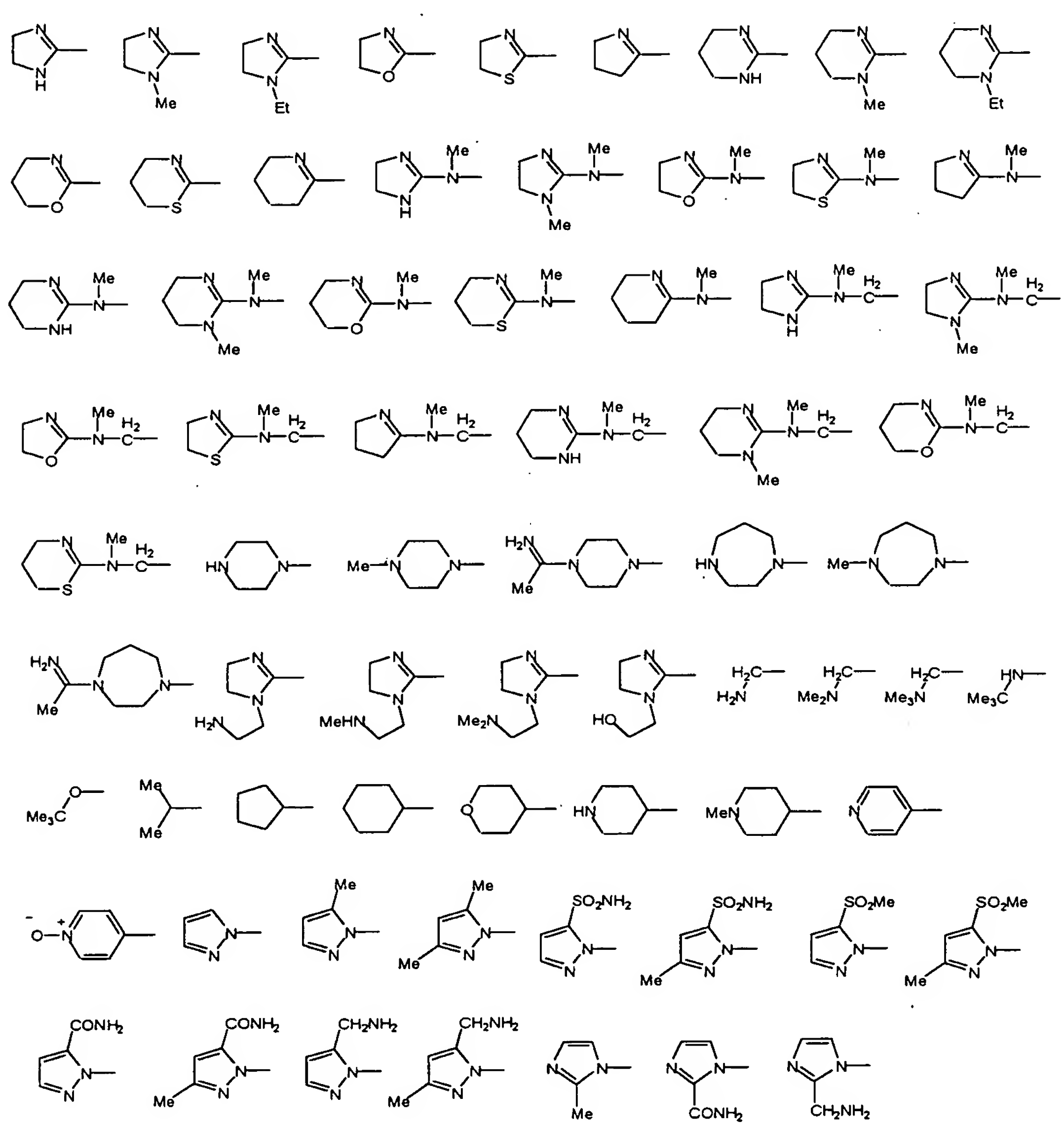
R^{1b3} is selected from the group consisting of $-Cl$, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 31

wherein:

A-Q is selected from the group consisting of:



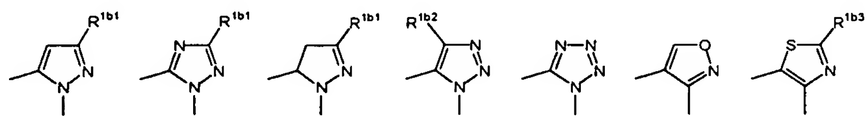
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $–NH_2$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, -Br, -OH, $-OCH_3$, and $–NH_2$;

G is selected from the group consisting of:



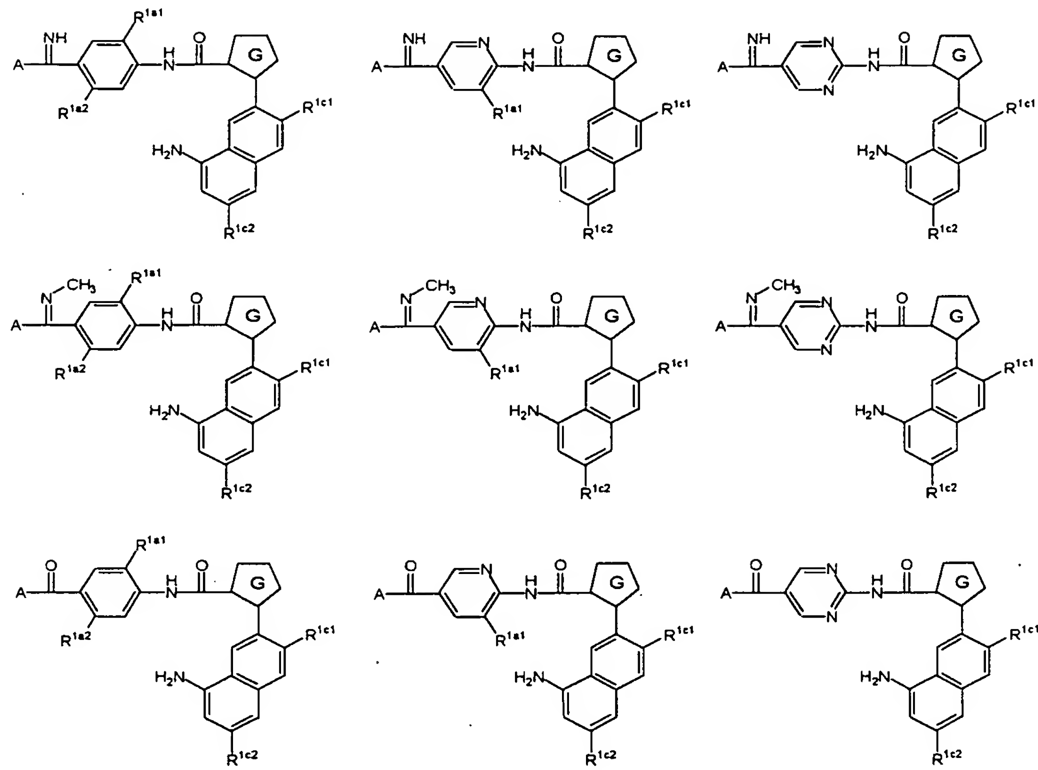
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $–CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $–CF_3$;

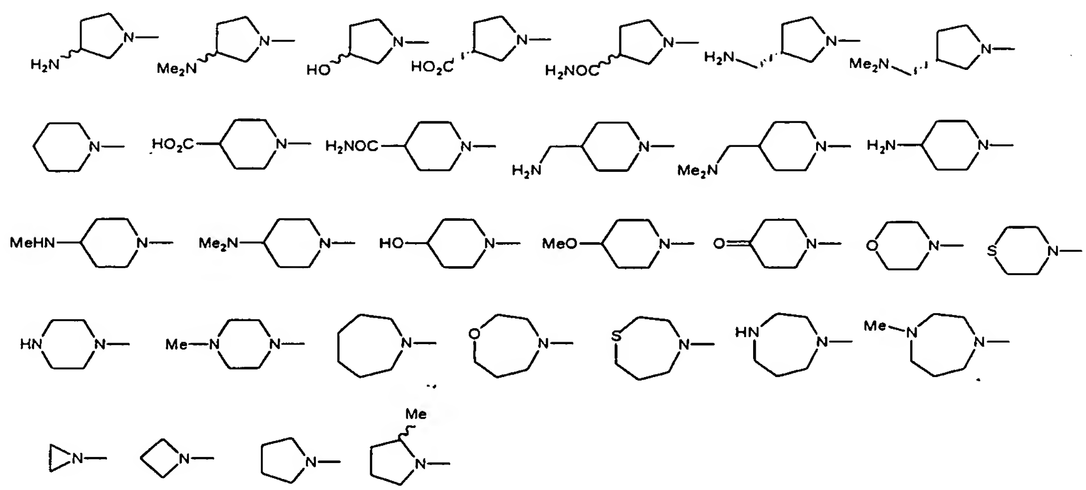
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $–CF_3$.

Table 32



wherein:

A is selected from the group consisting of:

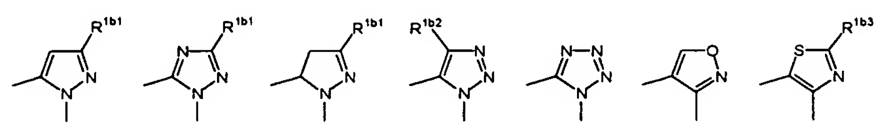


R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



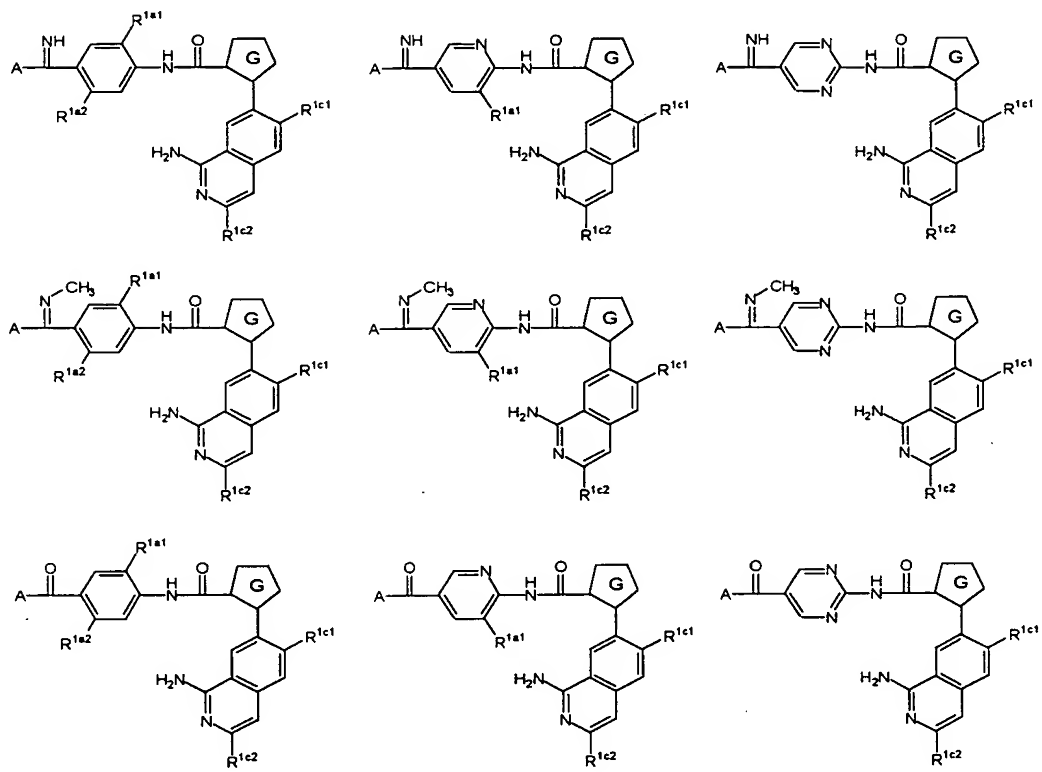
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

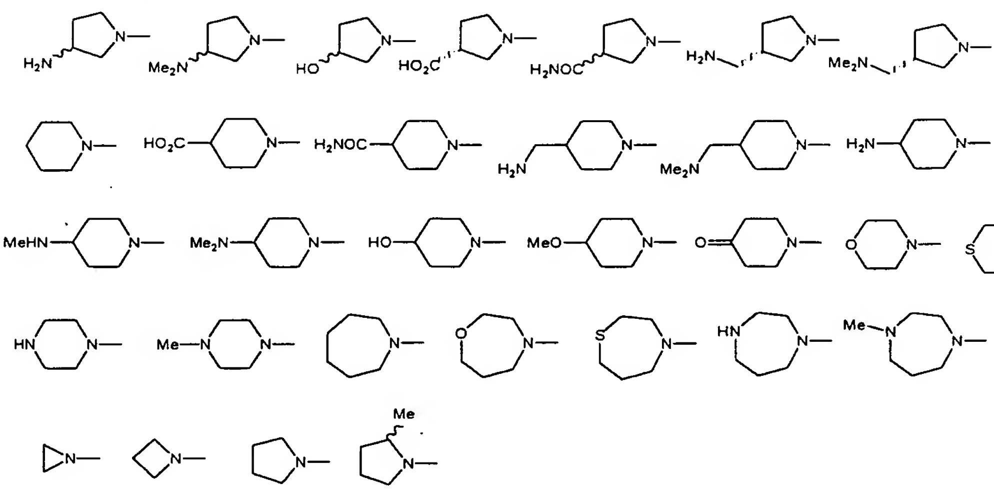
R^{1b3} is selected from the group consisting of $-Cl$, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 33



wherein:

A is selected from the group consisting of:

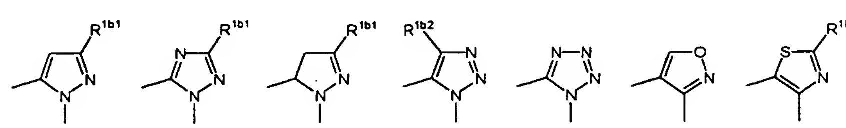


R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



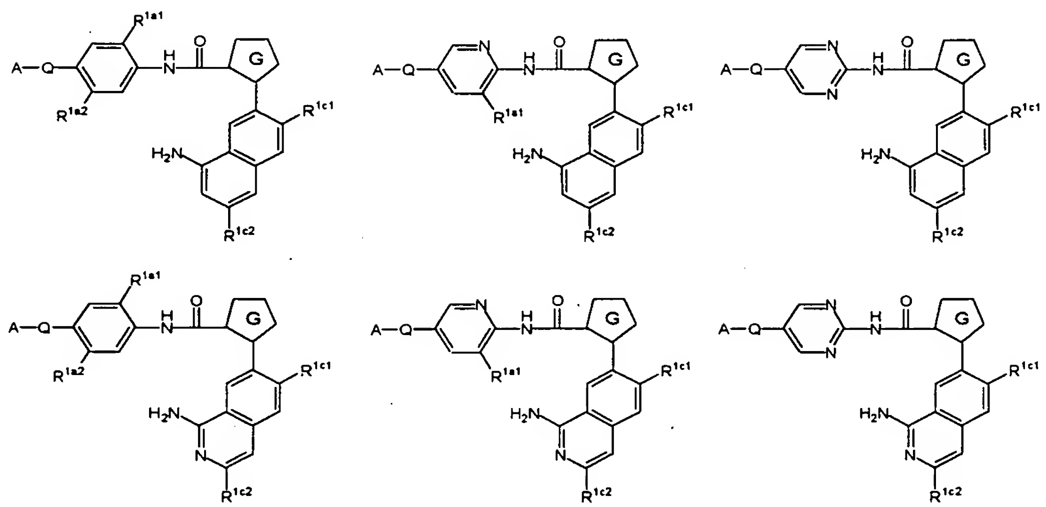
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

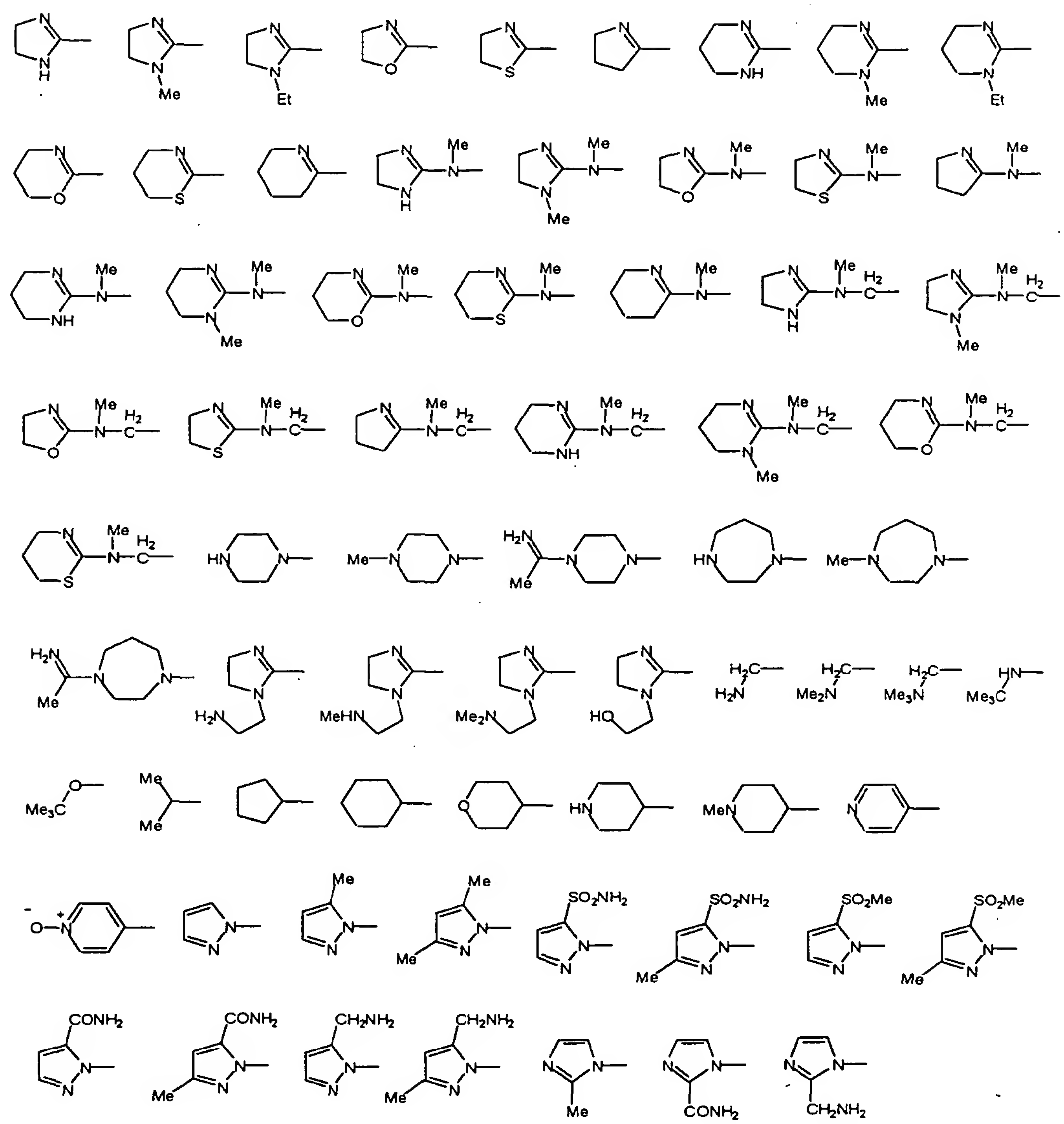
R^{1b3} is selected from the group consisting of $-Cl$, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 34



wherein:

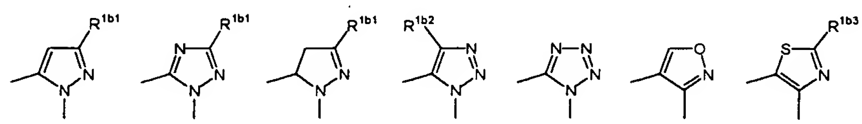
A-Q is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;



G is selected from the group consisting of:

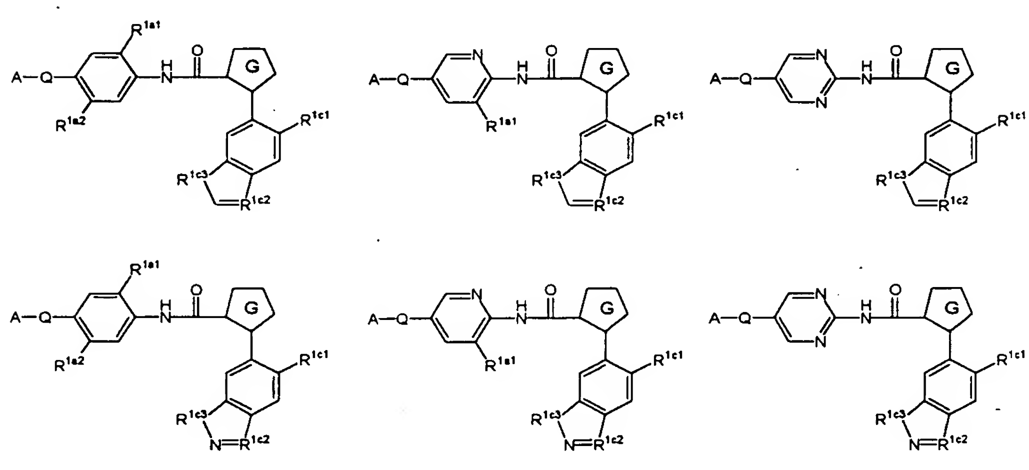
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

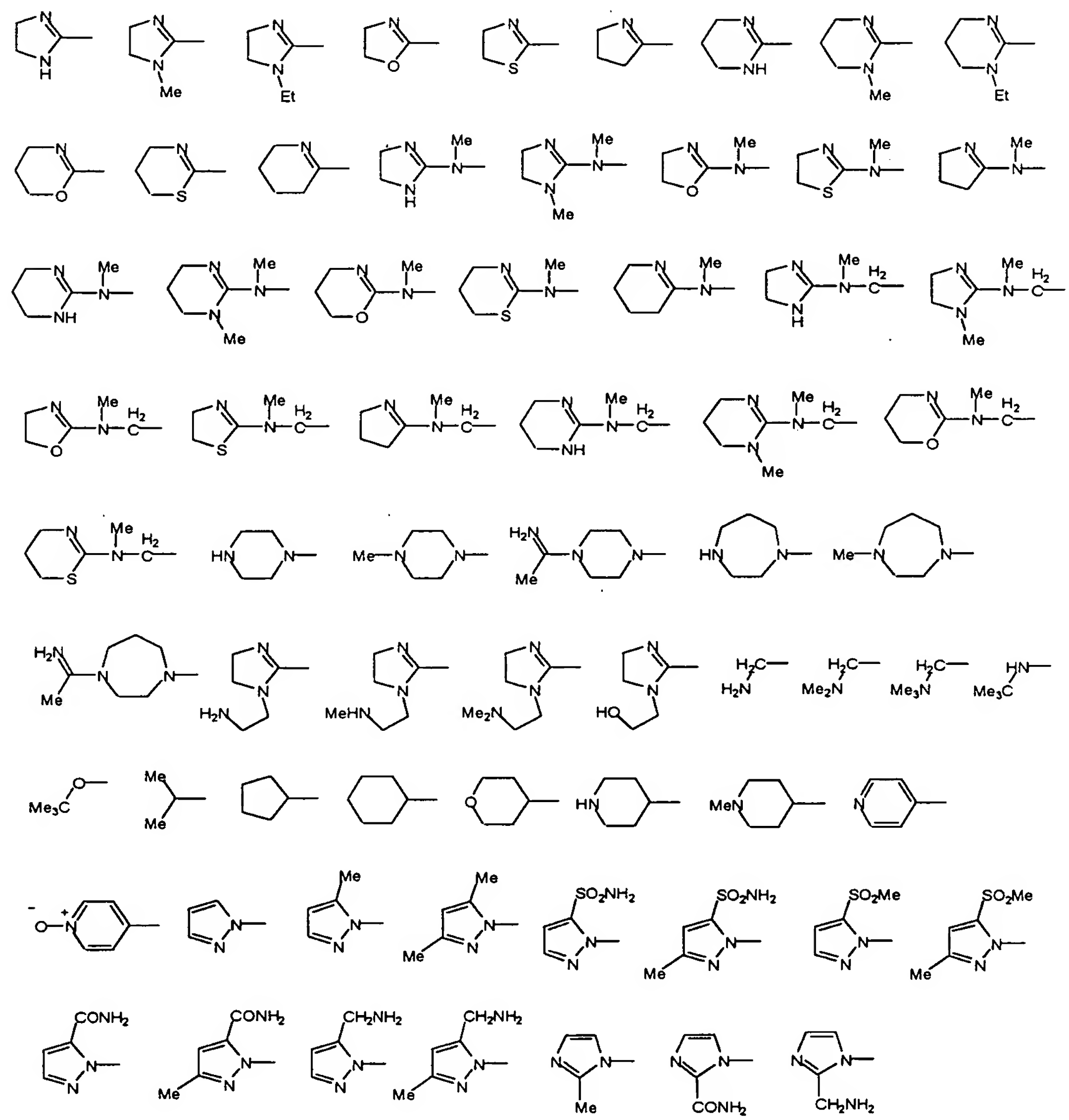
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

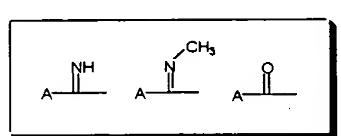
Table 35



wherein:

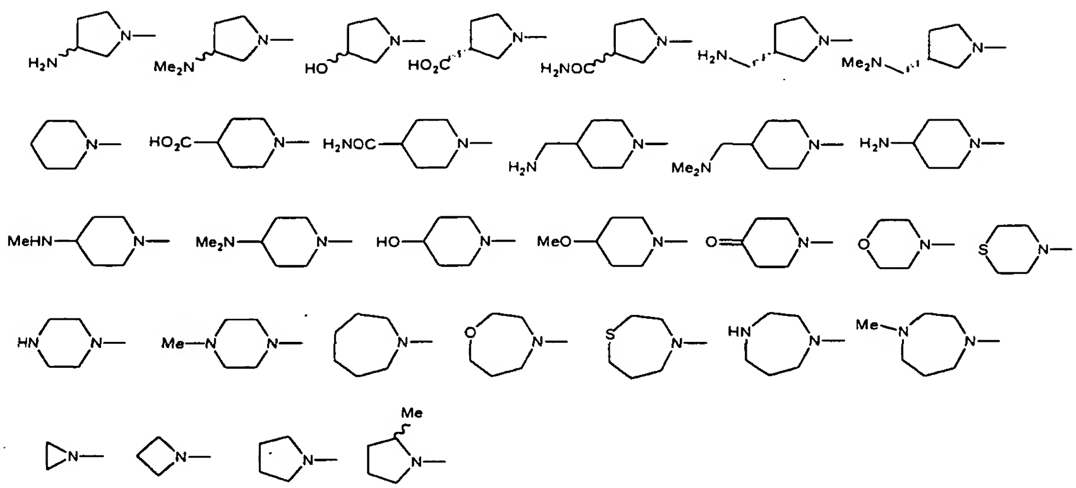
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:

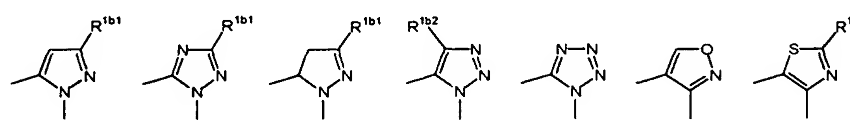


R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



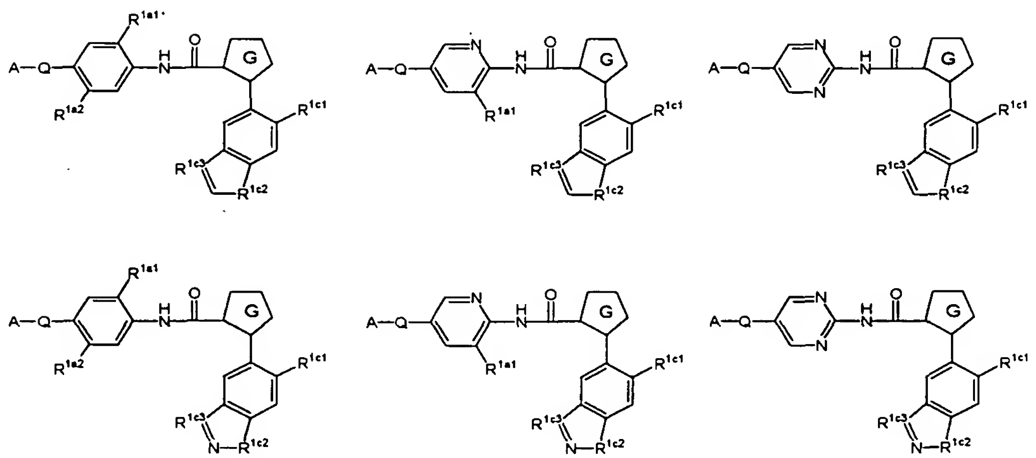
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

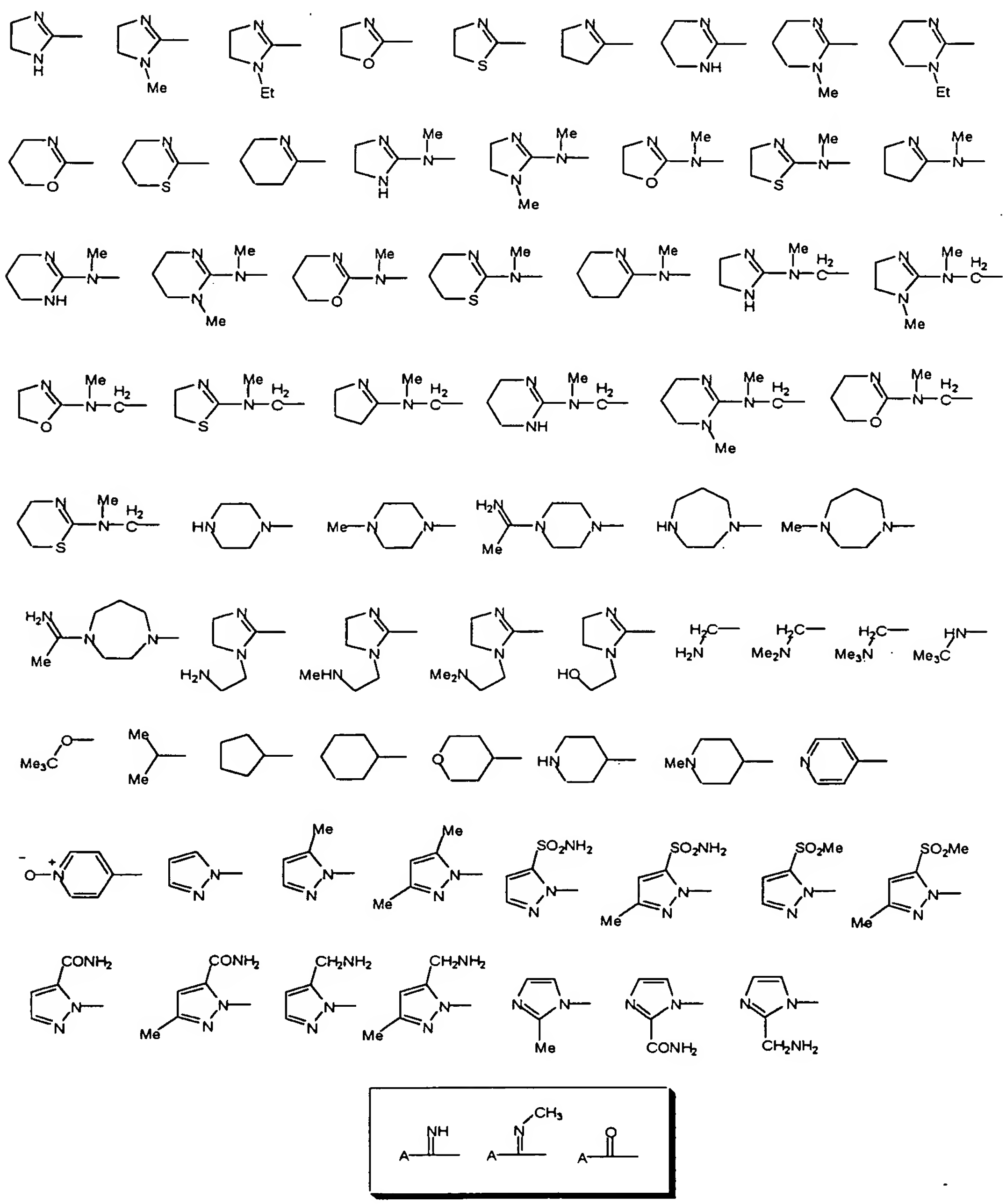
R^{1b3} is selected from the group consisting of $-Cl$, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 36



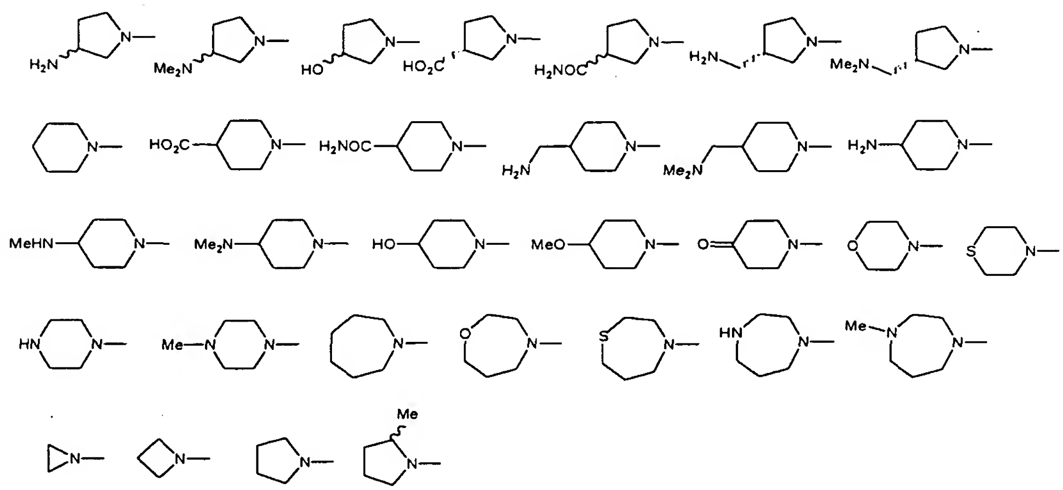
wherein:

A-Q is selected from the group consisting of:



wherein:

A is selected from the group consisting of:



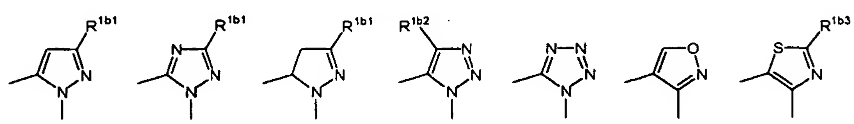
R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of $-CH_2-$, -O- and –NH-;

R^{1c3} is selected from the group consisting of –CH-, $-C(NH_2)-$ and –N-;

G is selected from the group consisting of:



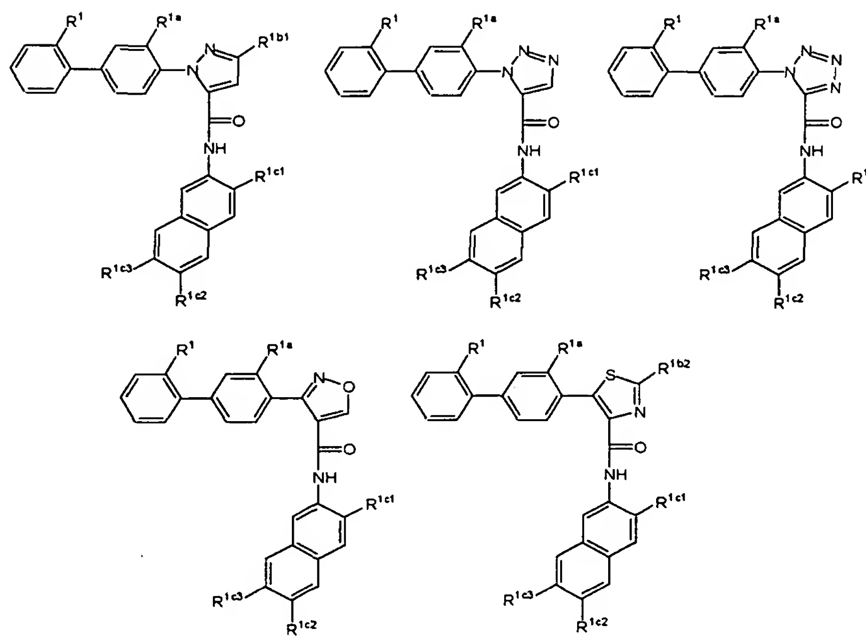
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

Table 37



wherein:

R^1 is selected from the group consisting of -SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

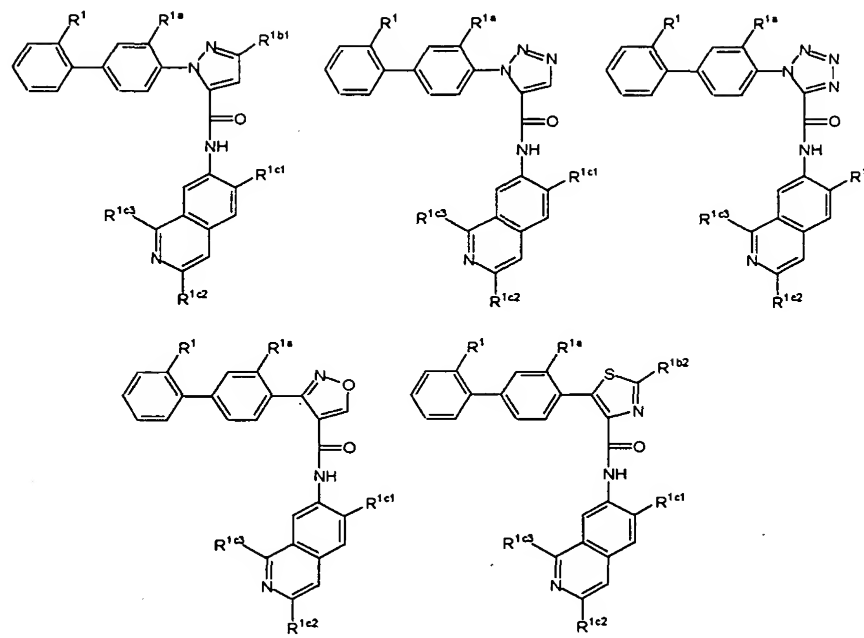
R^{1b2} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –H, -F, -Cl and -Br;

R^{1c3} is selected from the group consisting of –H, -F, -Cl and –Br.

Table 38



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, –CN, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

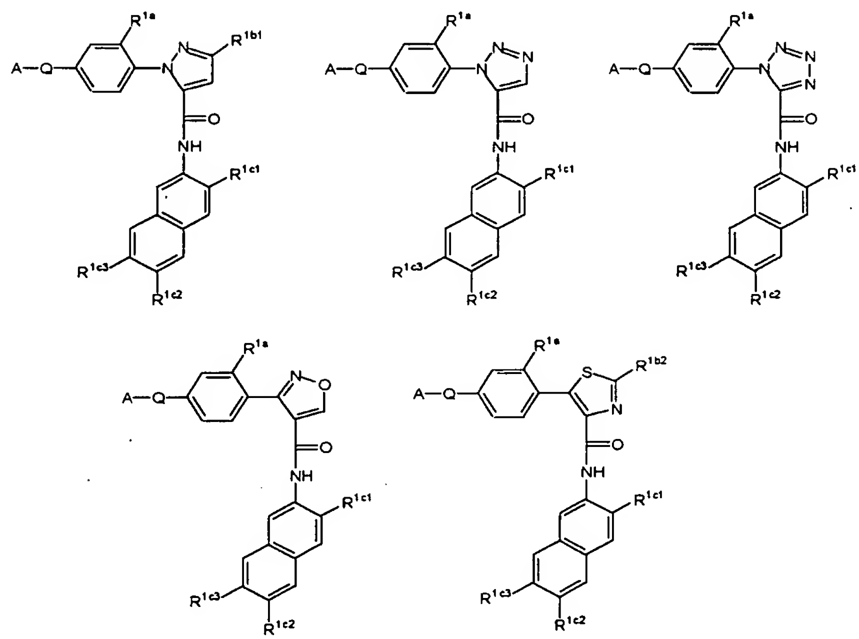
R^{1b2} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl and -Br;

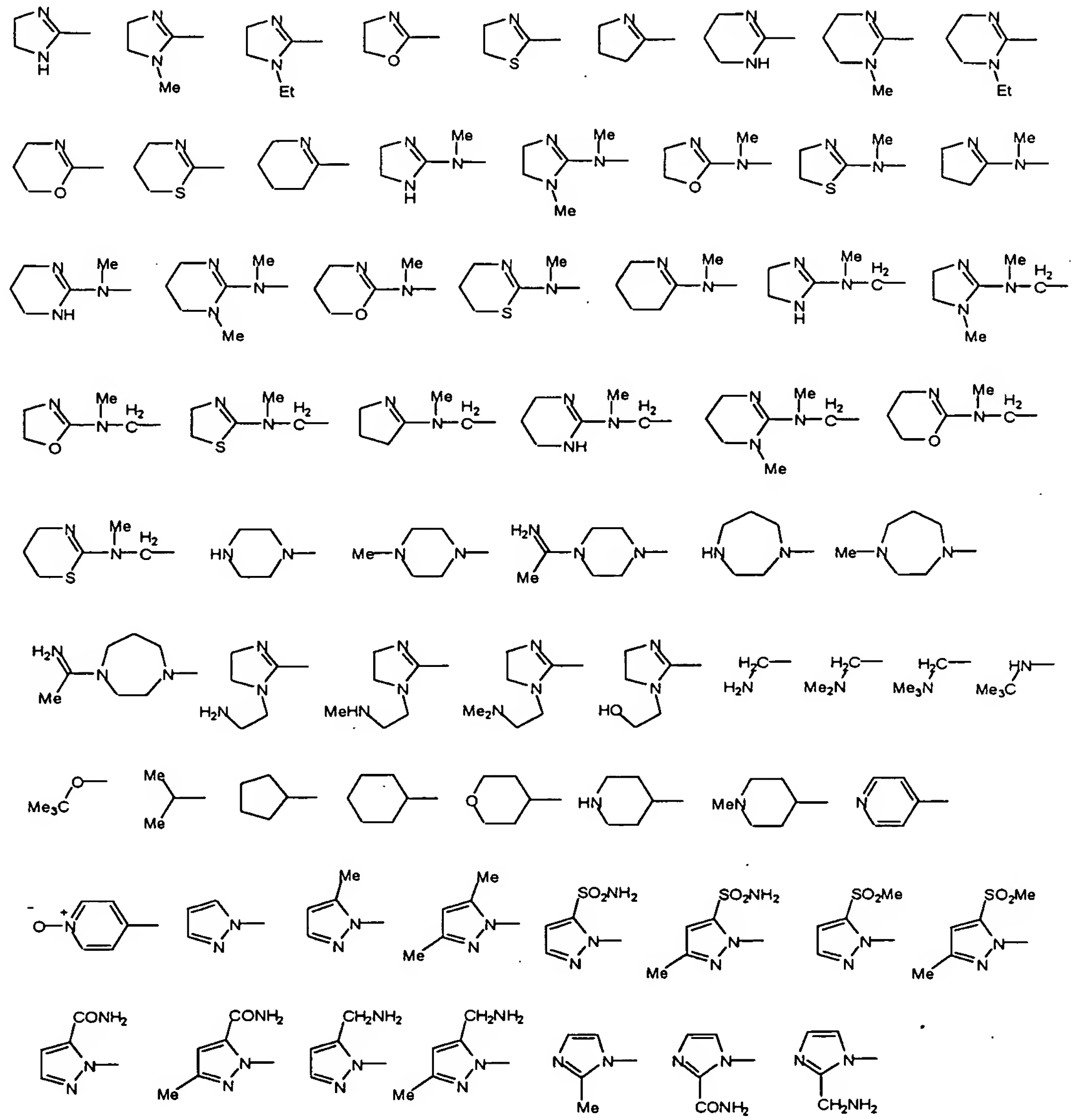
R^{1c3} is selected from the group consisting of –H and –NH_2.

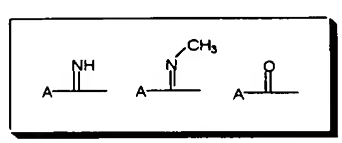
Table 39



wherein:

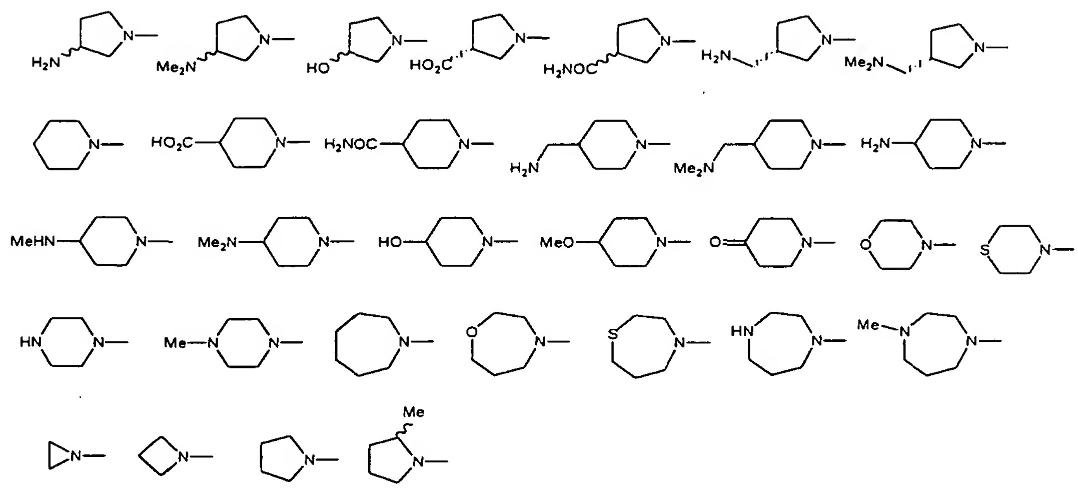
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $–CF_3$;

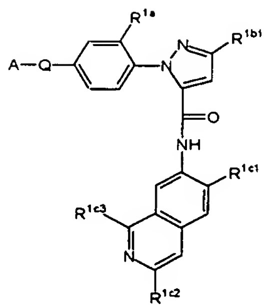
R^{1b2} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $–CF_3$;

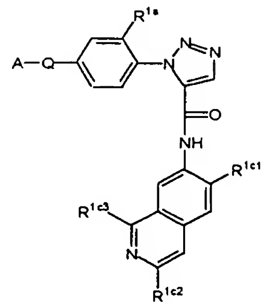
R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

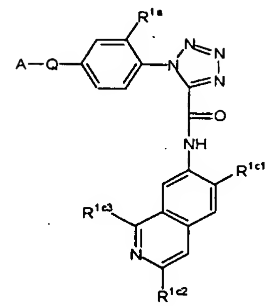
R^{1c2} is selected from the group consisting of –H, -F, -Cl and -Br;

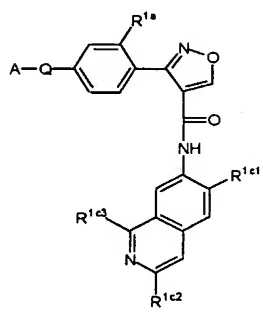
R^{1c3} is selected from the group consisting of –H, -F, -Cl and –Br.

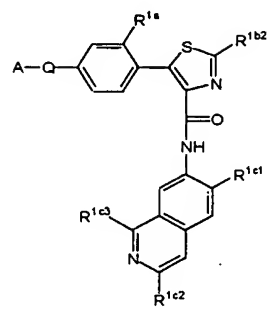
Table 40





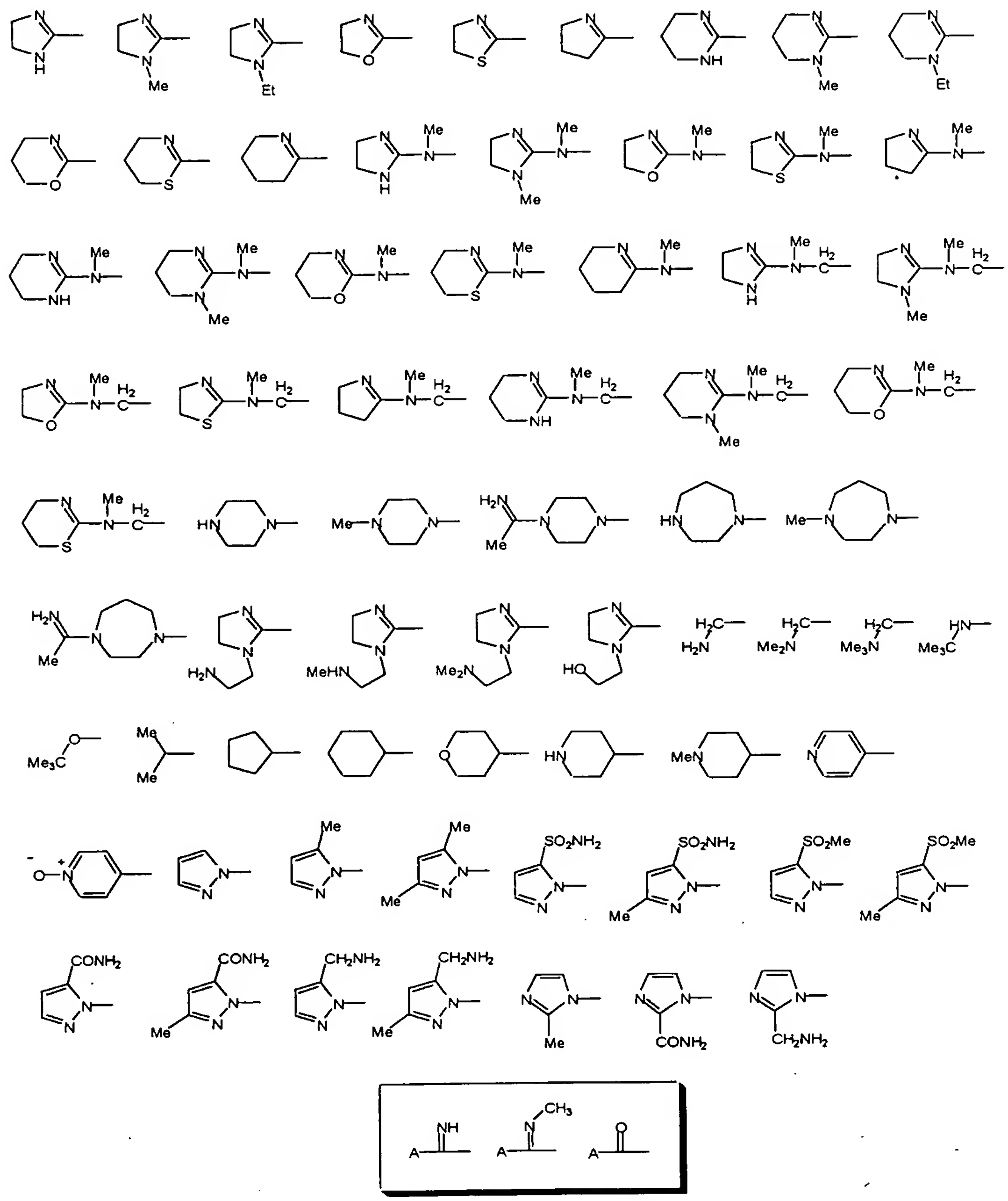






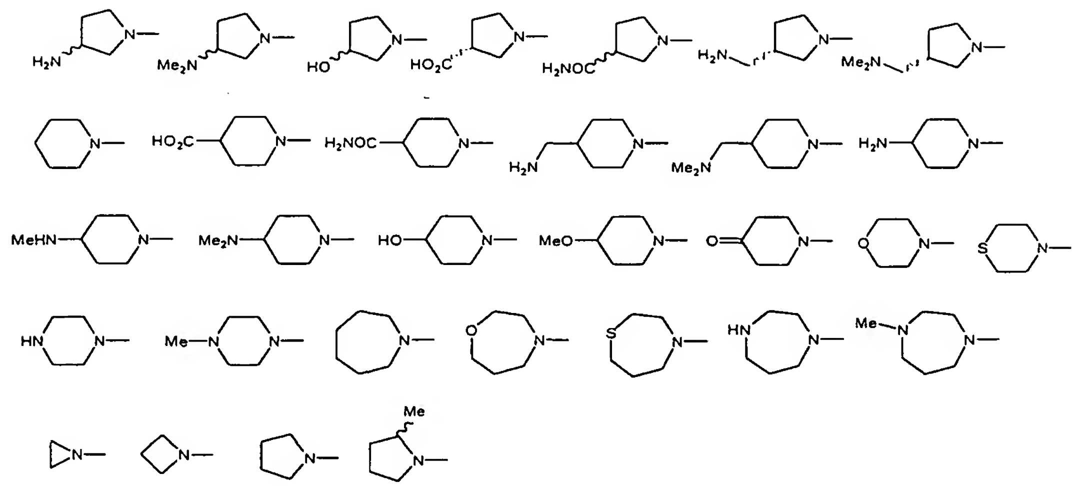
wherein:

A-Q is selected from the group consisting of:



wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

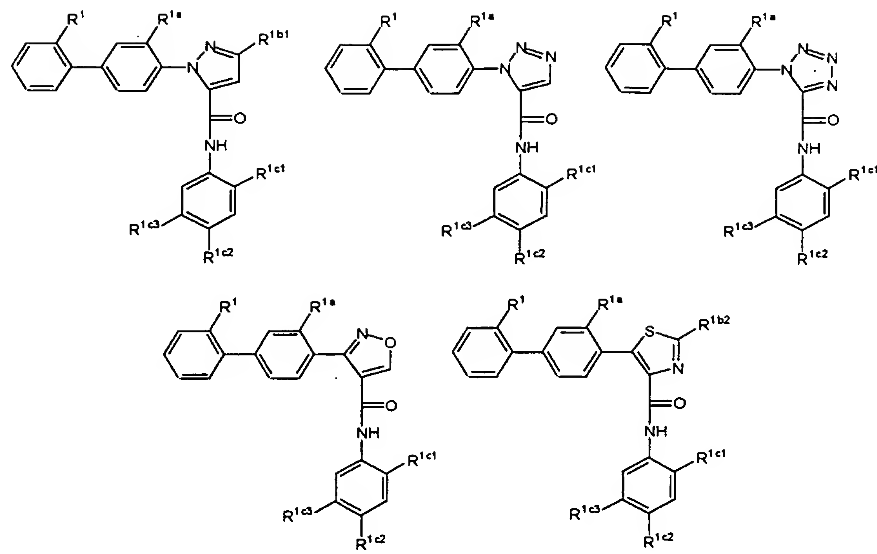
R^{1b2} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3;

R^{1c1} is selected from the group consisting of –H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

R^{1c2} is selected from the group consisting of –H, -F, -Cl and -Br;

R^{1c3} is selected from the group consisting of –H and –NH_2.

Table 41



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

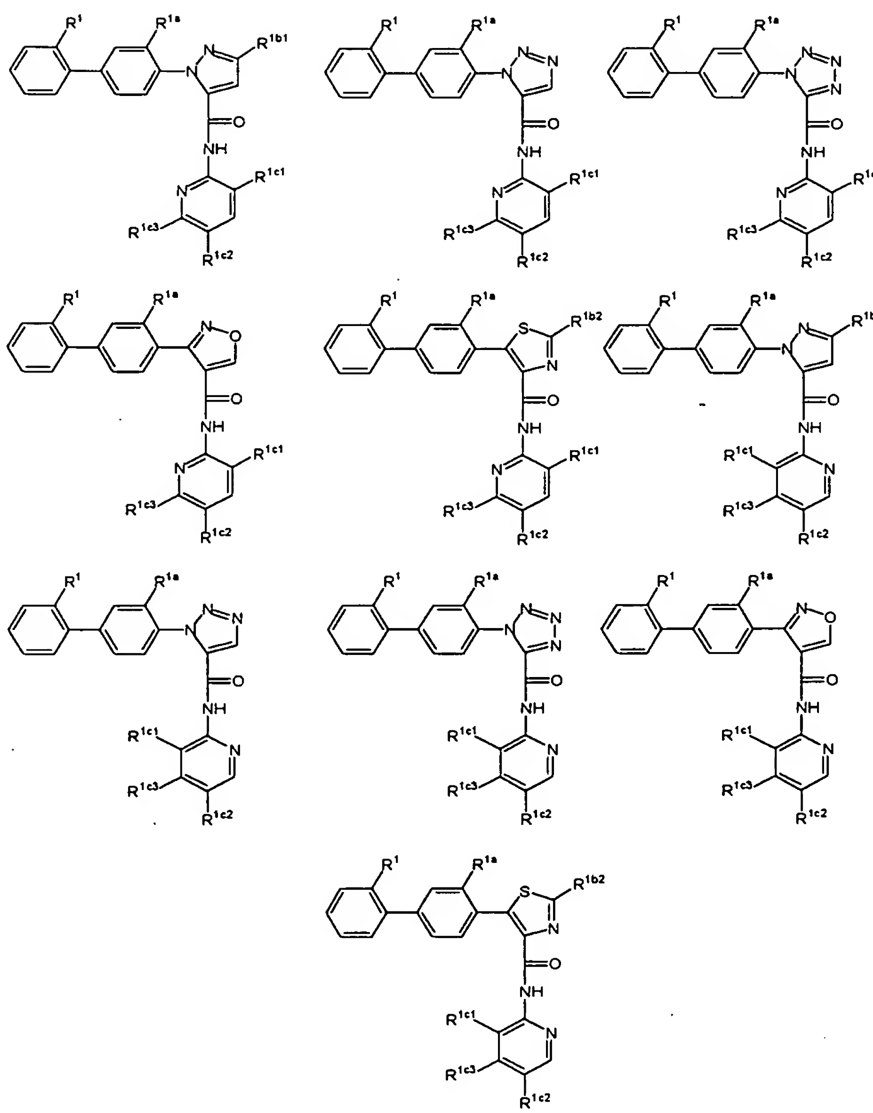
R^{1b2} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -CN, $-CH_2NH_2$, $-CONH_2$, $-SO_2Me$, $-SO_2NH_2$ and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, Br, $-OCH_3$, $-CH_2NH_2$, $-CONH_2$ and $-C(N{=}H)NH_2$.

Table 42



wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

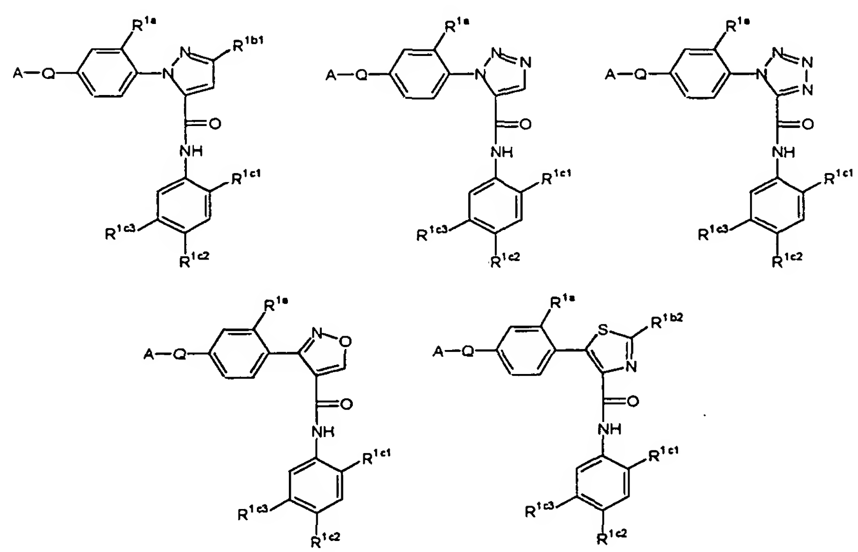
R^{1b2} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -CN, $-CH_2NH_2$, $-CONH_2$, $-SO_2Me$, $-SO_2NH_2$ and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br and $-OCH_3$;

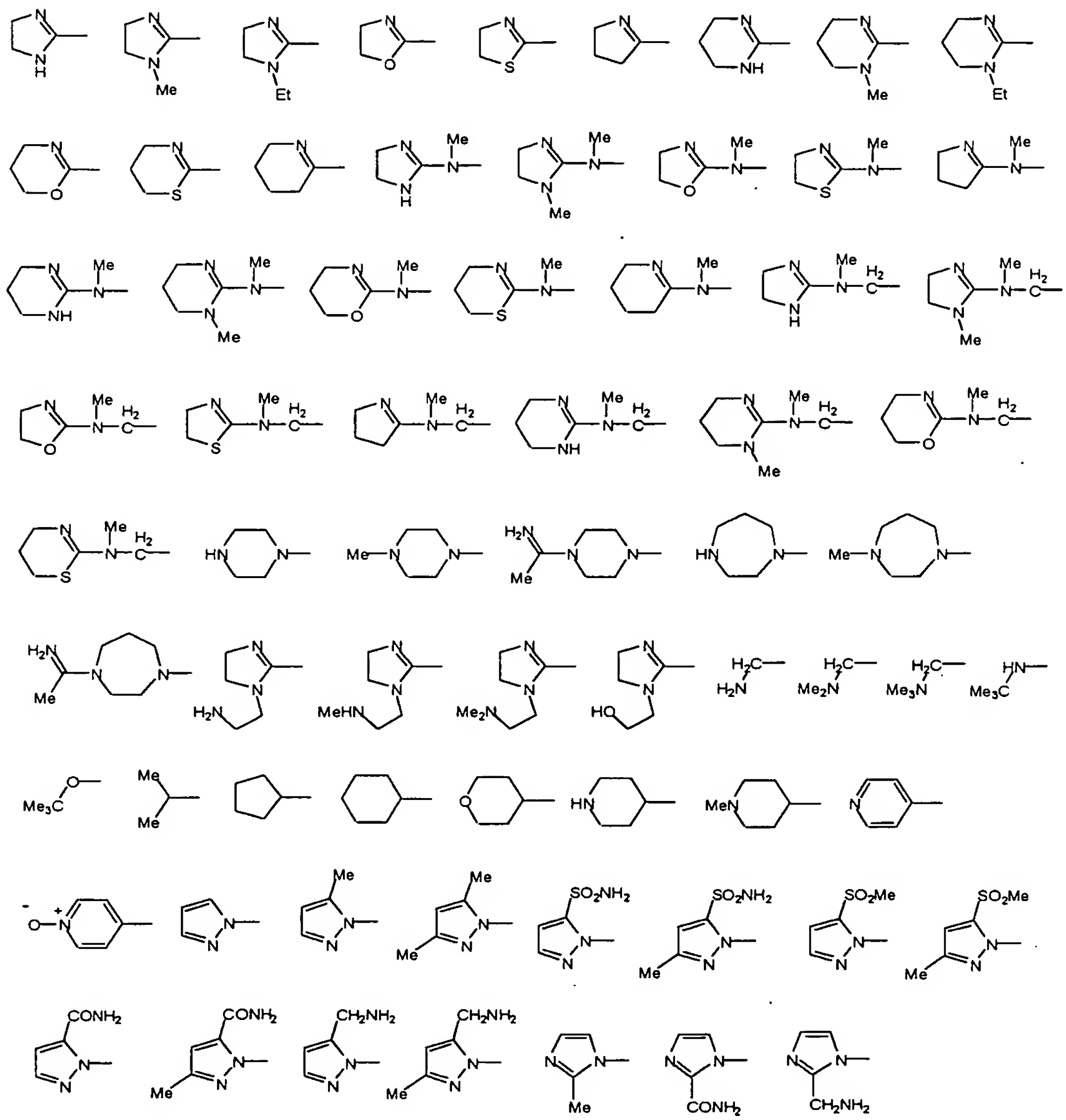
R^{1c3} is selected from the group consisting of –H, -F, -Cl, Br, $-OCH_3$, $-CH_2NH_2$, $-CONH_2$ and $-C(N{=}H)NH_2$.

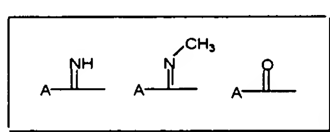
Table 43



wherein:

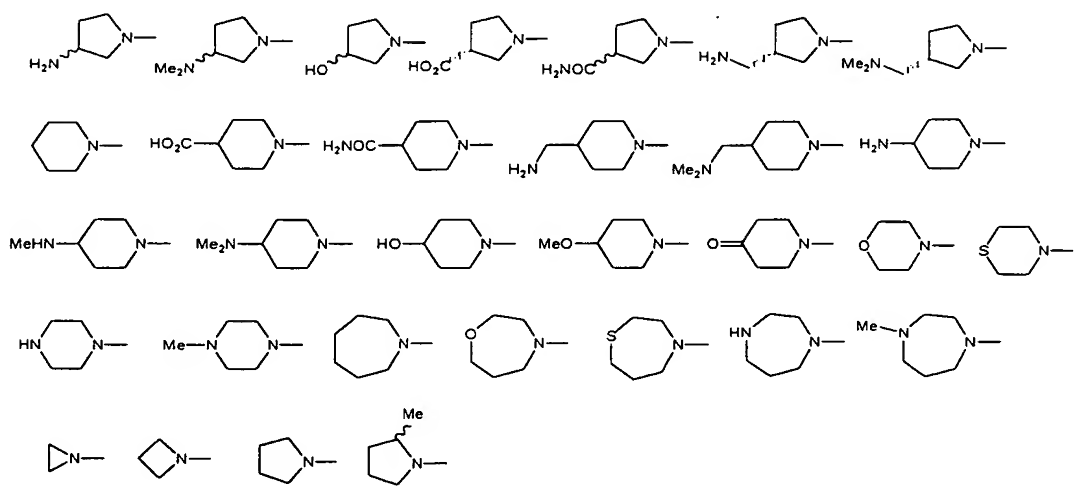
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



wherein:

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $–CF_3$;

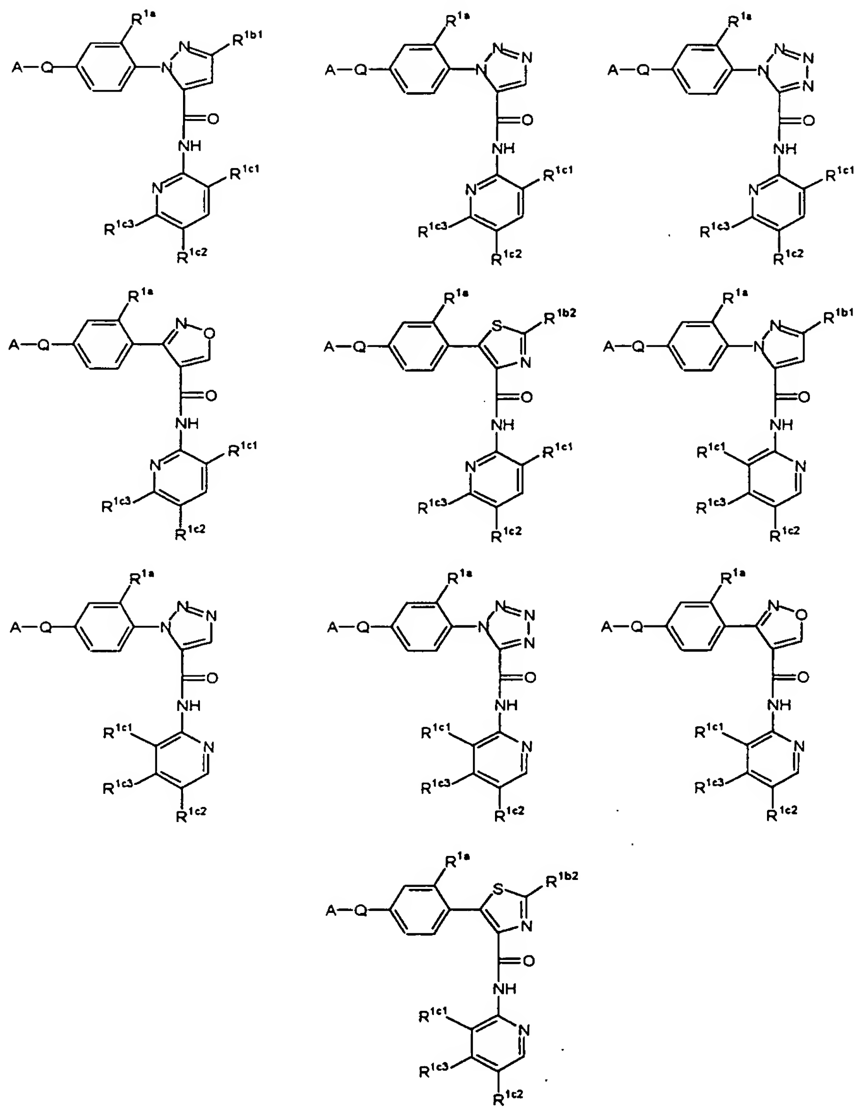
R^{1b2} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $–CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -CN, $-CH_2NH_2$, $-CONH_2$, $-SO_2Me$, $-SO_2NH_2$ and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br and $–OCH_3$;

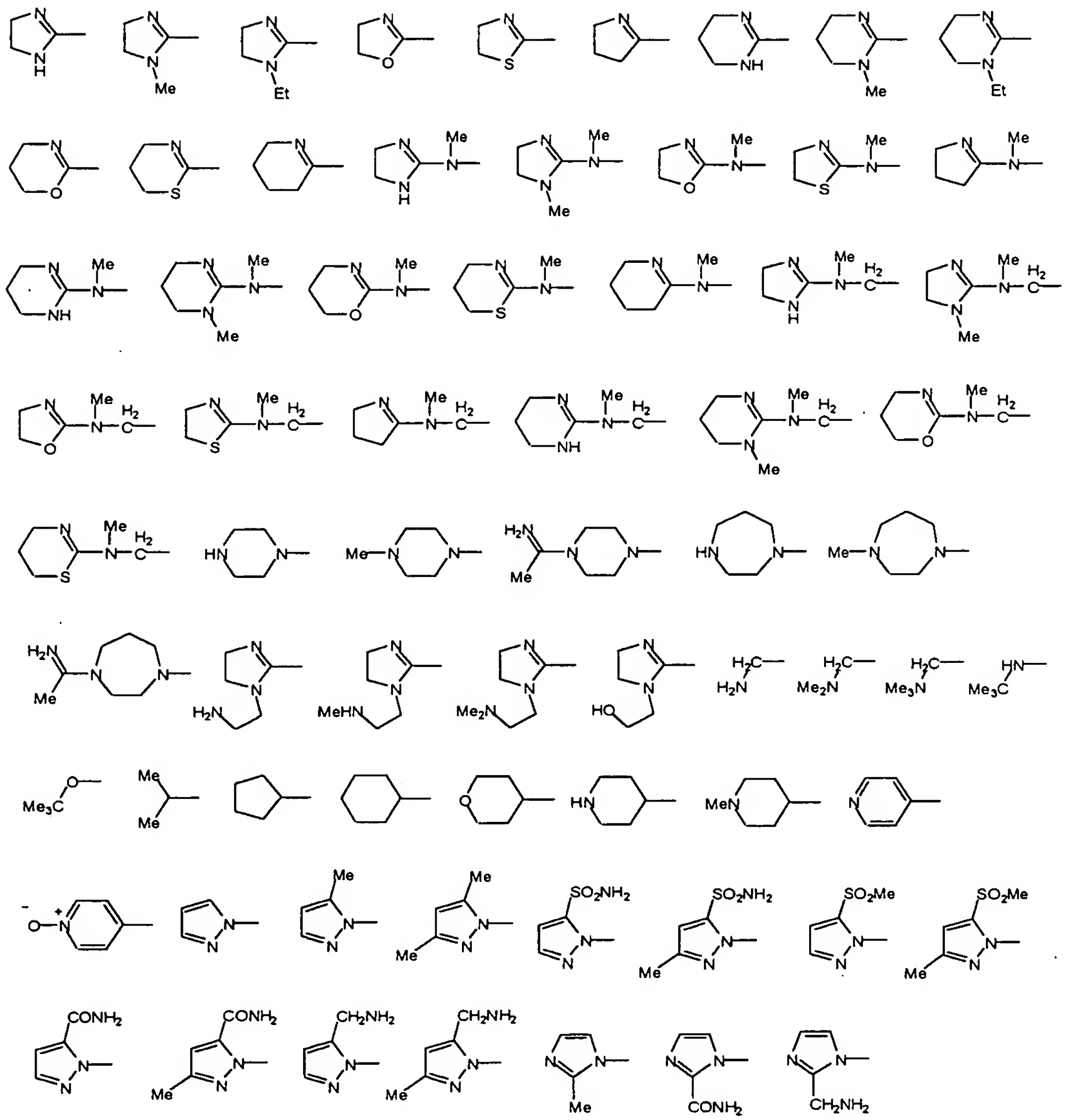
R^{1c3} is selected from the group consisting of –H, -F, -Cl, Br, $-OCH_3$, $-CH_2NH_2$, $-CONH_2$ and $-C(N{=}H)NH_2$.

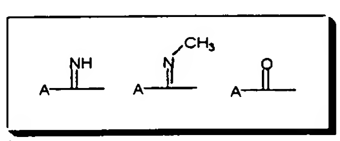
Table 44



wherein:

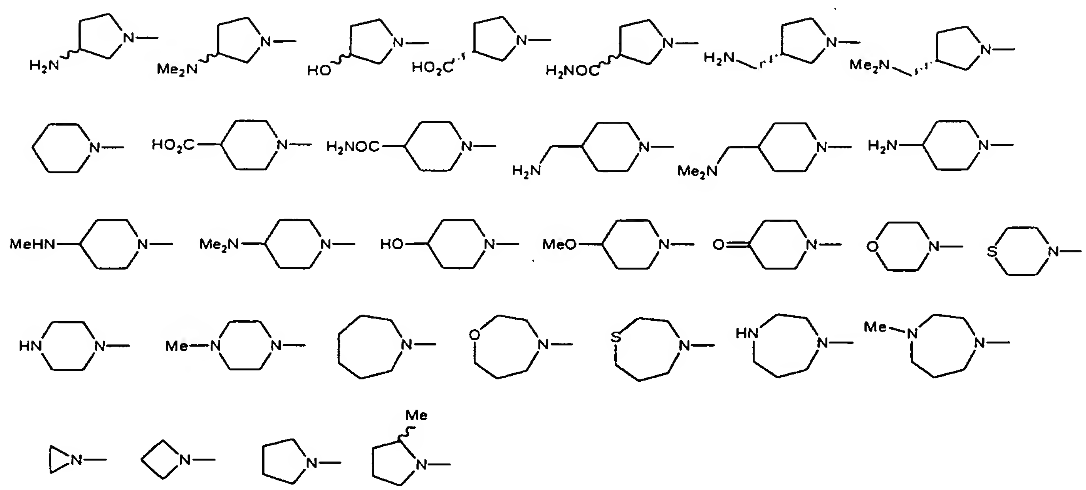
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



wherein:

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

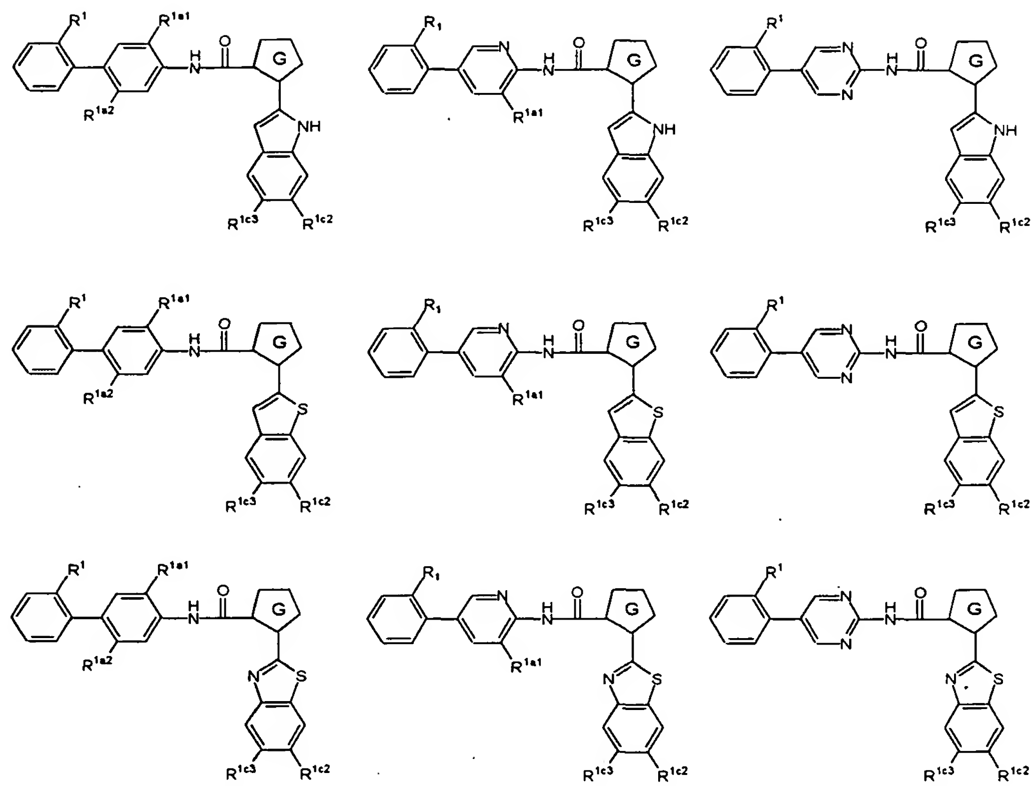
R^{1b2} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of –H, –F, -CN, $-CH_2NH_2$, $-CONH_2$, $-SO_2Me$, $-SO_2NH_2$ and $-NO_2$;

R^{1c2} is selected from the group consisting of –H, -F, -Cl, -Br and $-OCH_3$;

R^{1c3} is selected from the group consisting of –H, -F, -Cl, Br, $-OCH_3$, $-CH_2NH_2$, $-CONH_2$ and $-C(N{=}H)NH_2$.

Table 45



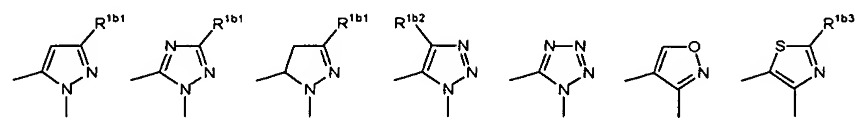
wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, –CN, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



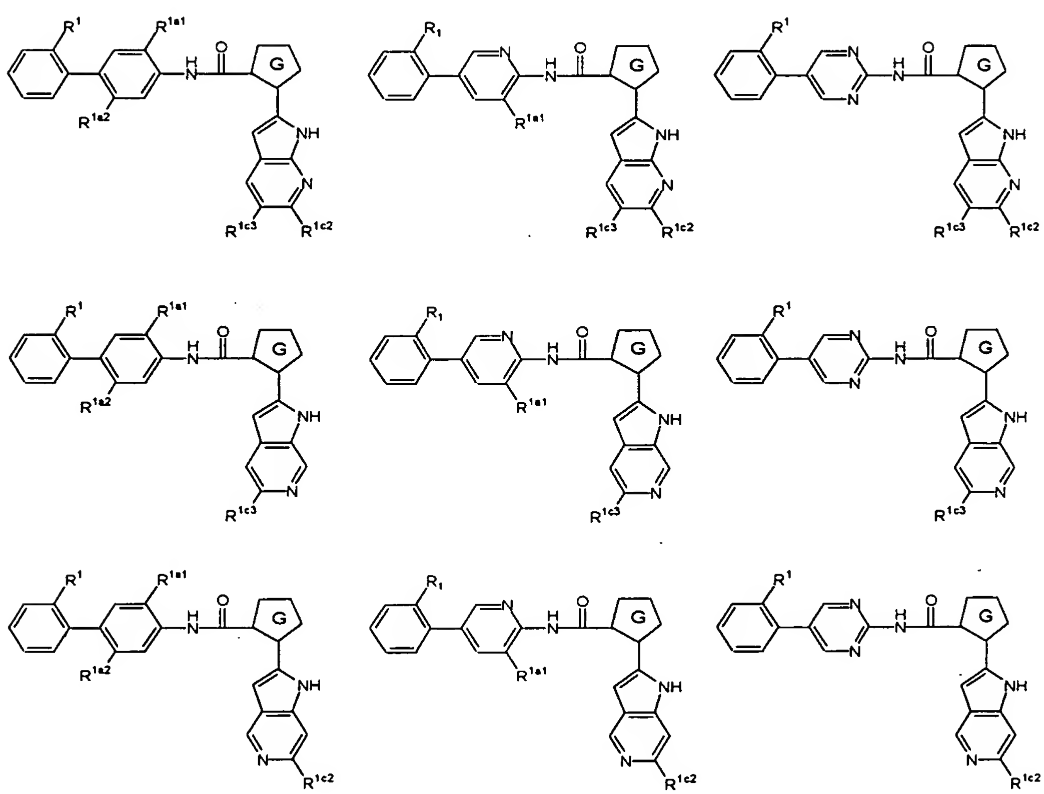
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 46



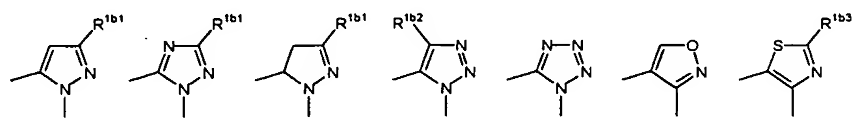
wherein:

R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



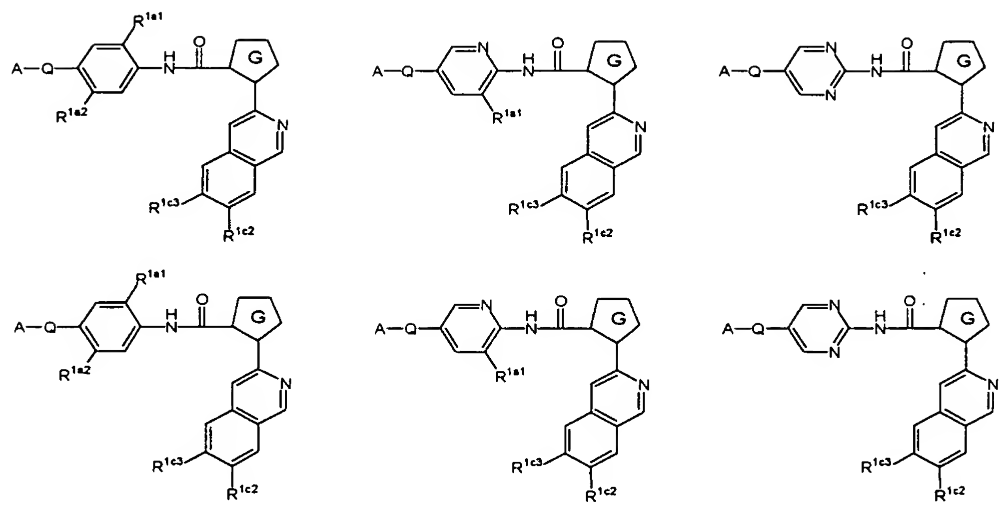
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

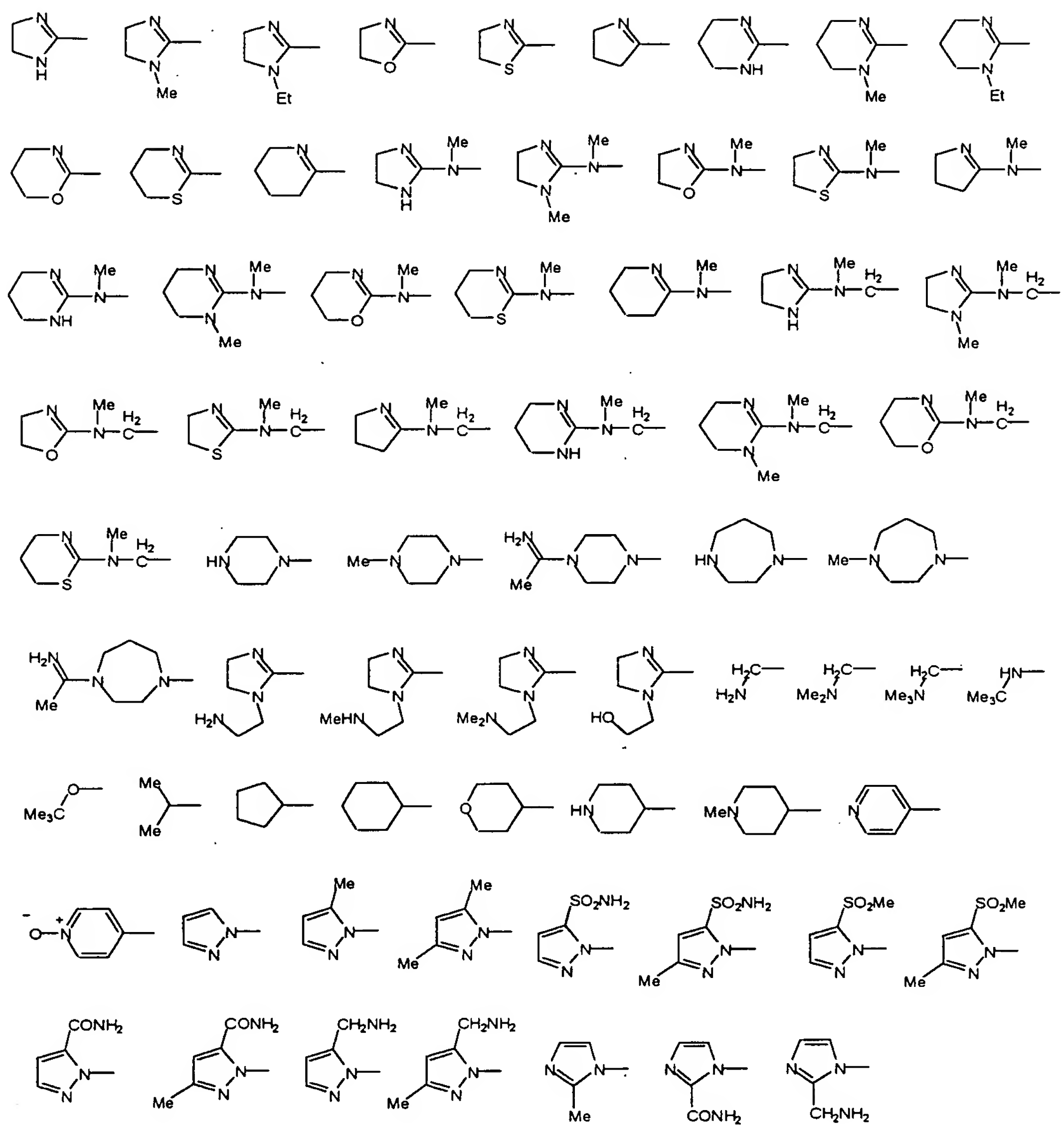
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

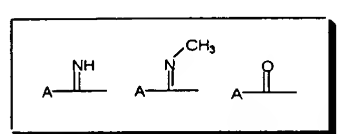
Table 47



wherein:

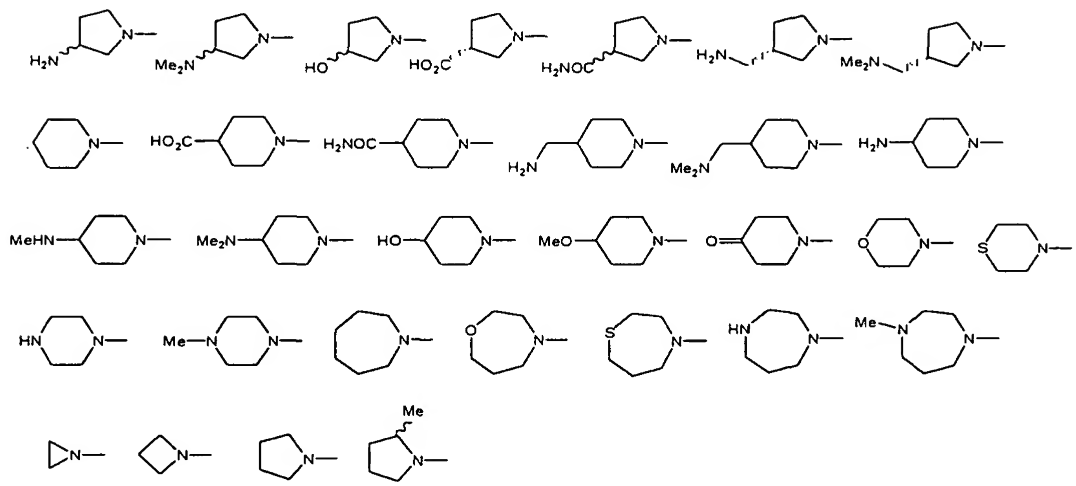
A-Q is selected from the group consisting of:





wherein:

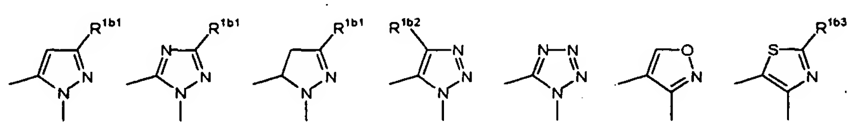
A is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and -OCH_3;

G is selected from the group consisting of:



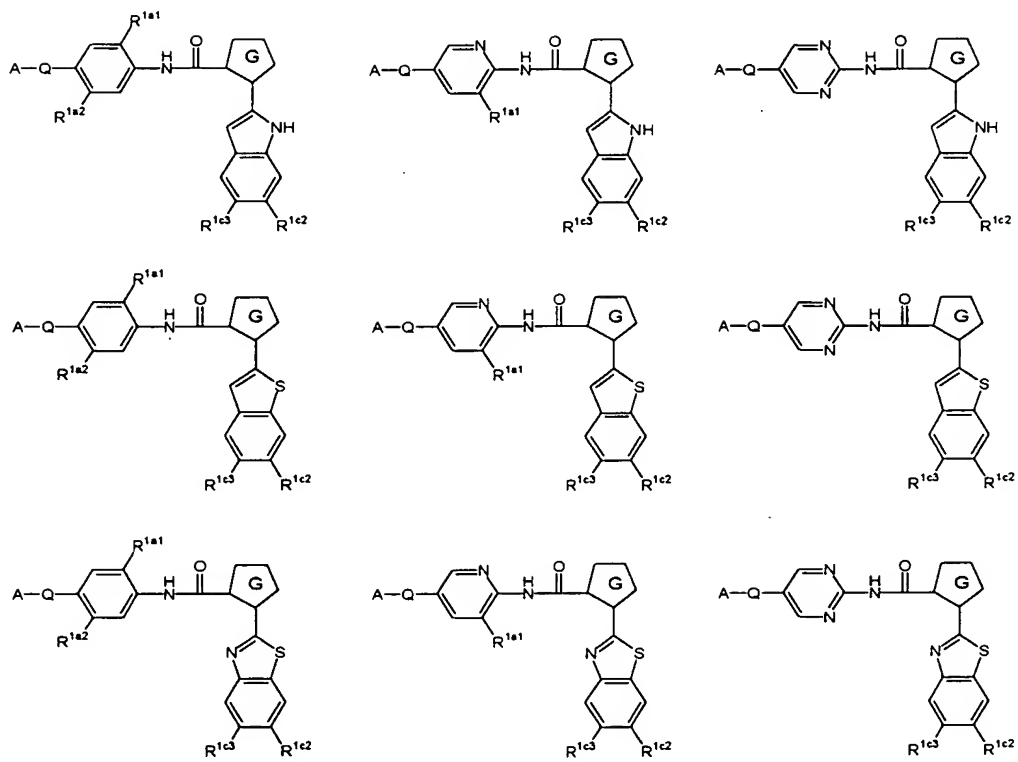
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

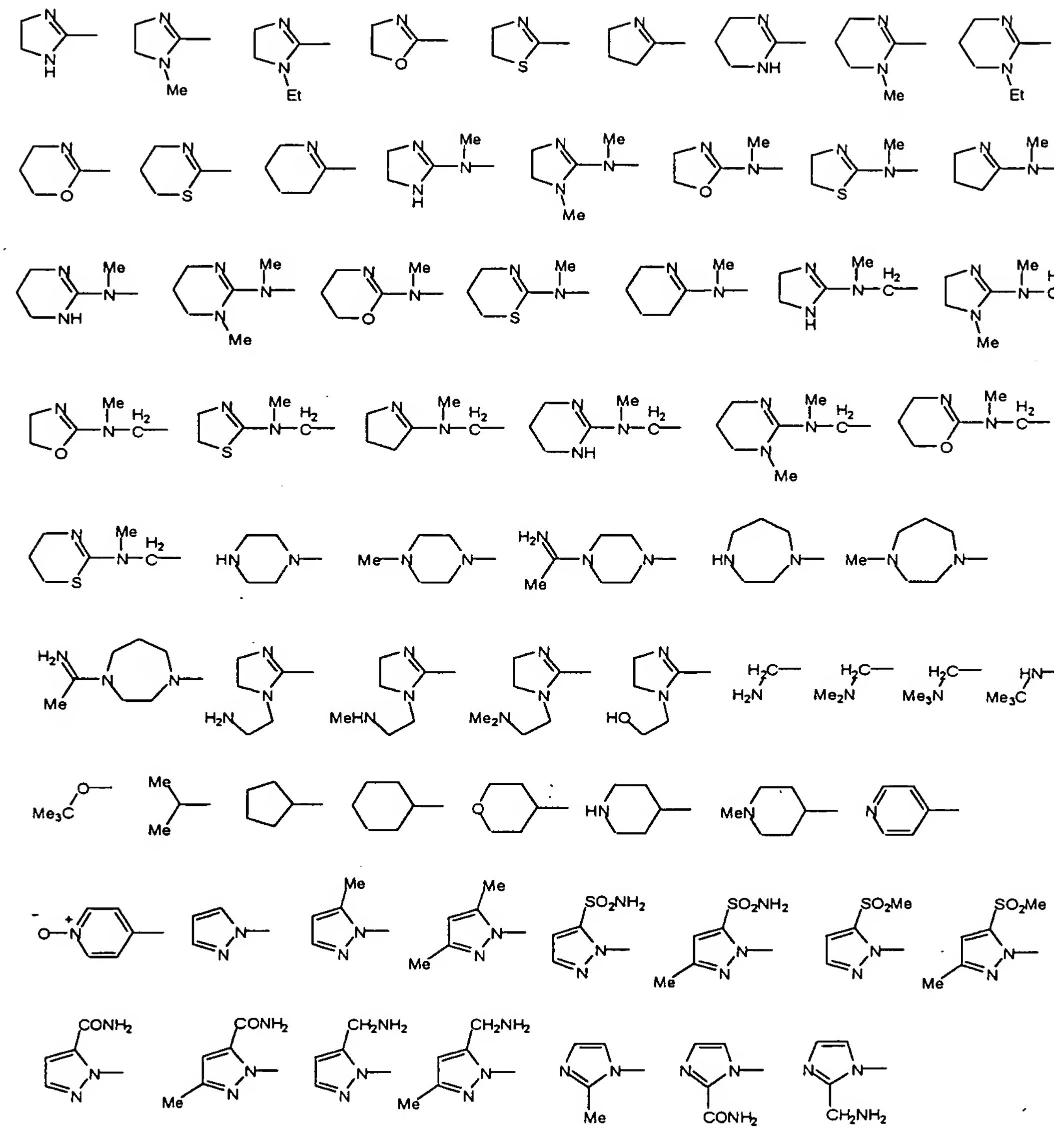
R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

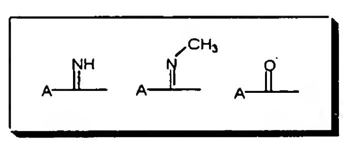
Table 48



wherein:

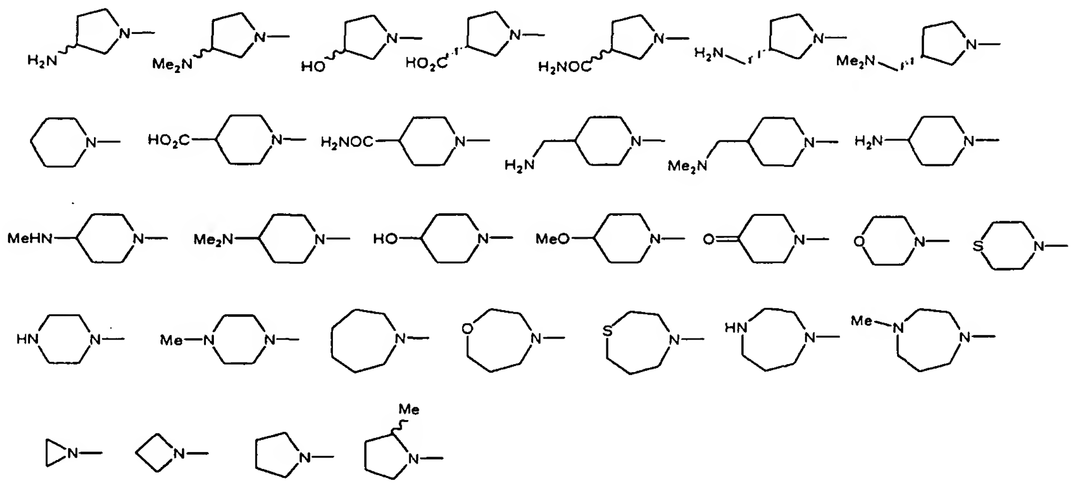
A-Q is selected from the group consisting of:





wherein:

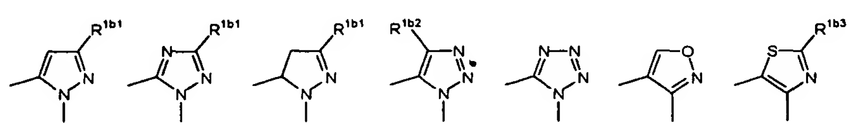
A is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and $-OCH_3$;

G is selected from the group consisting of:



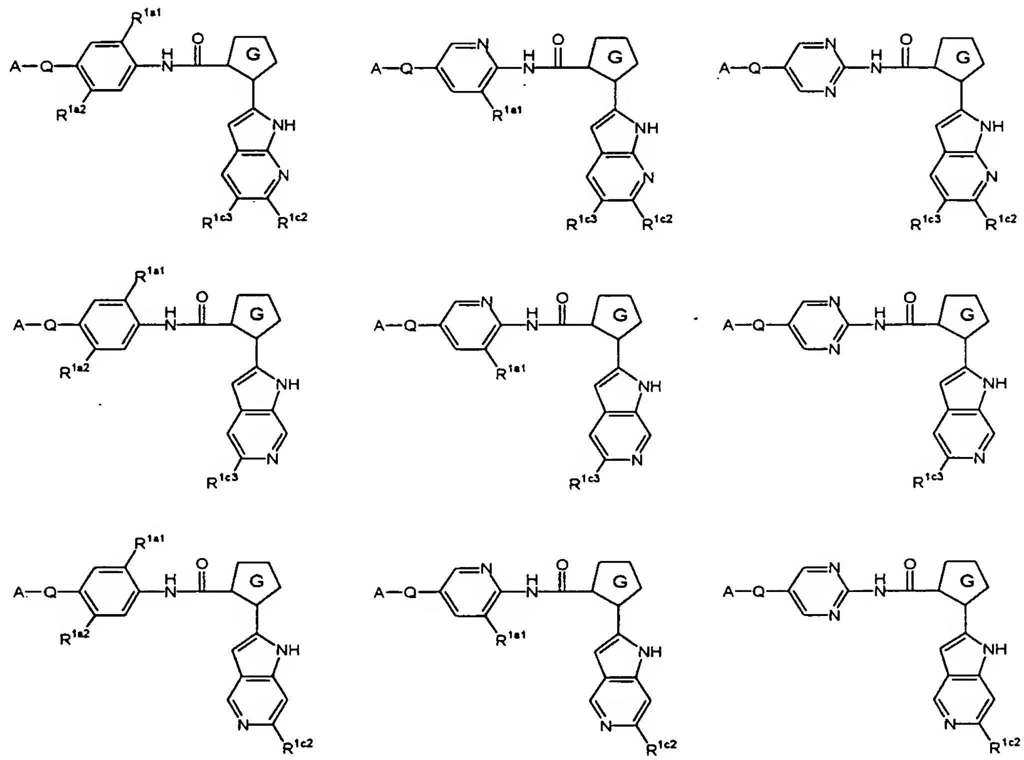
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

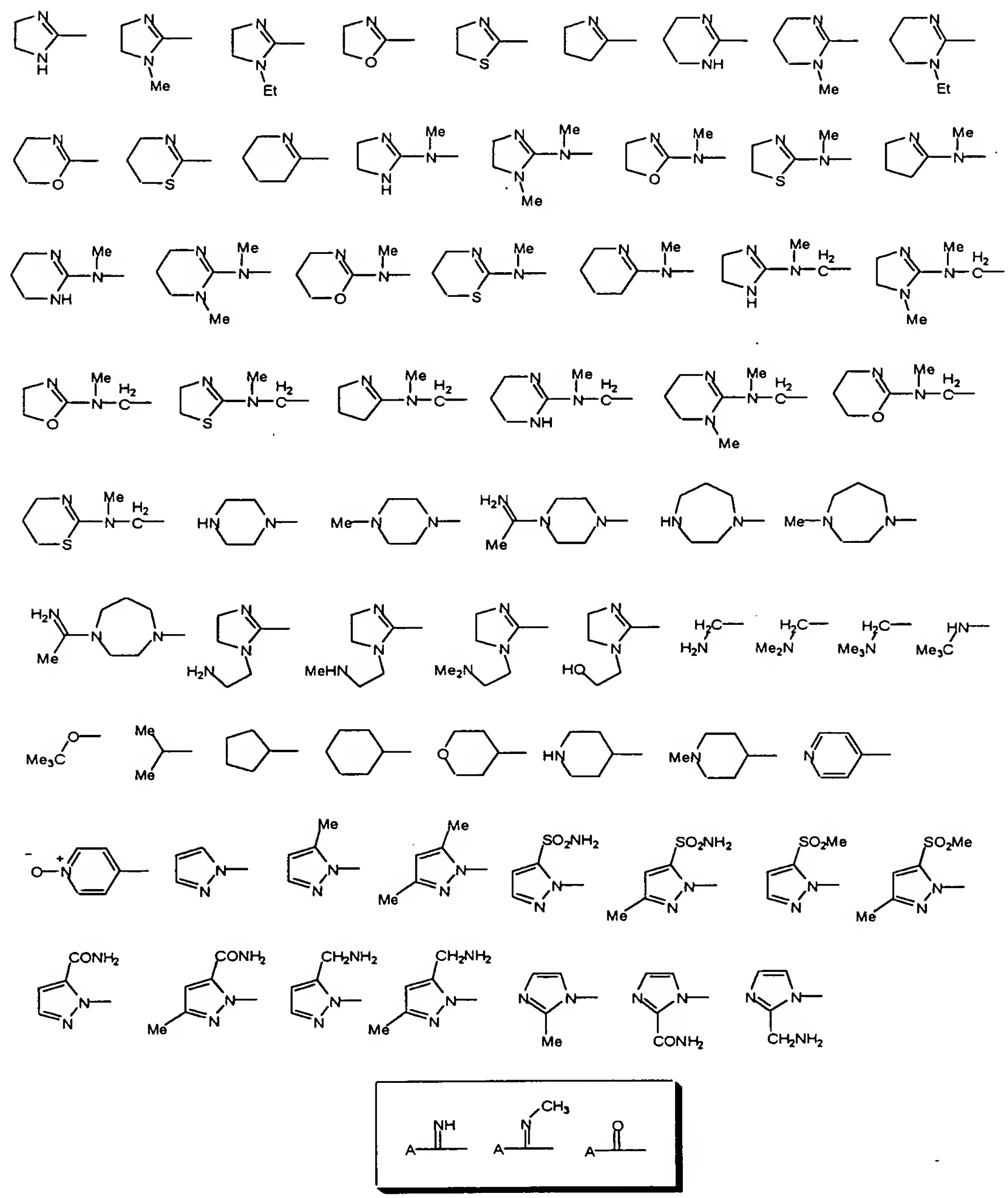
R^{1b3} is selected from the group consisting of $-Cl$, $-NH_2$, $-CH_3$ and $-CF_3$.

Table 49



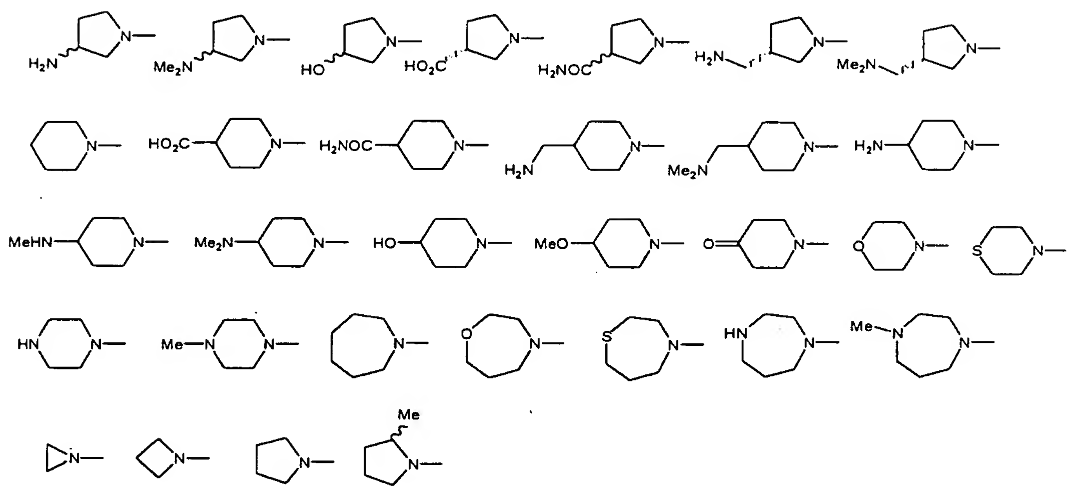
wherein:

A-Q is selected from the group consisting of:



wherein:

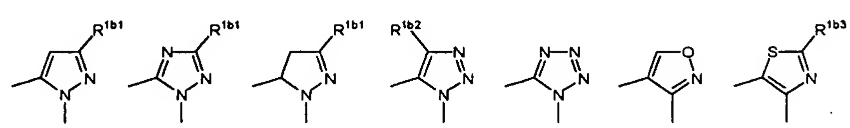
A is selected from the group consisting of:



R^{1a1} and R^{1a2} are independently selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and -OCH_3;

G is selected from the group consisting of:



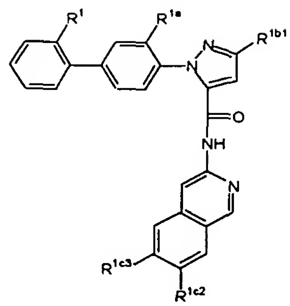
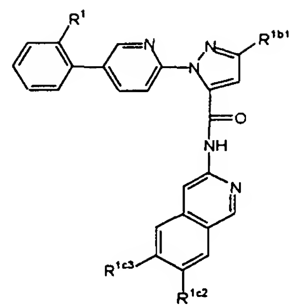
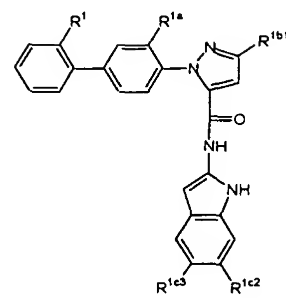
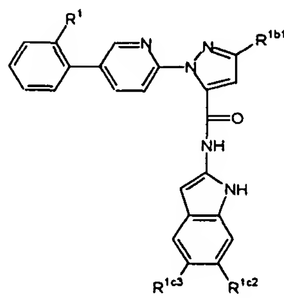
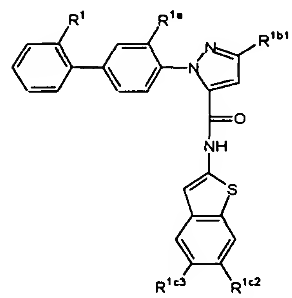
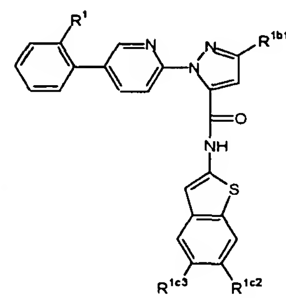
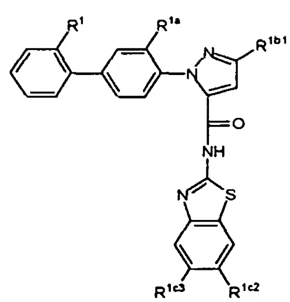
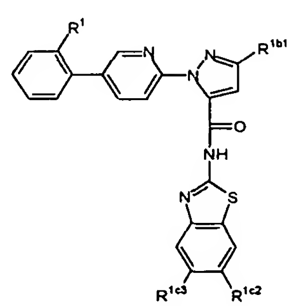
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

Table 50

wherein:

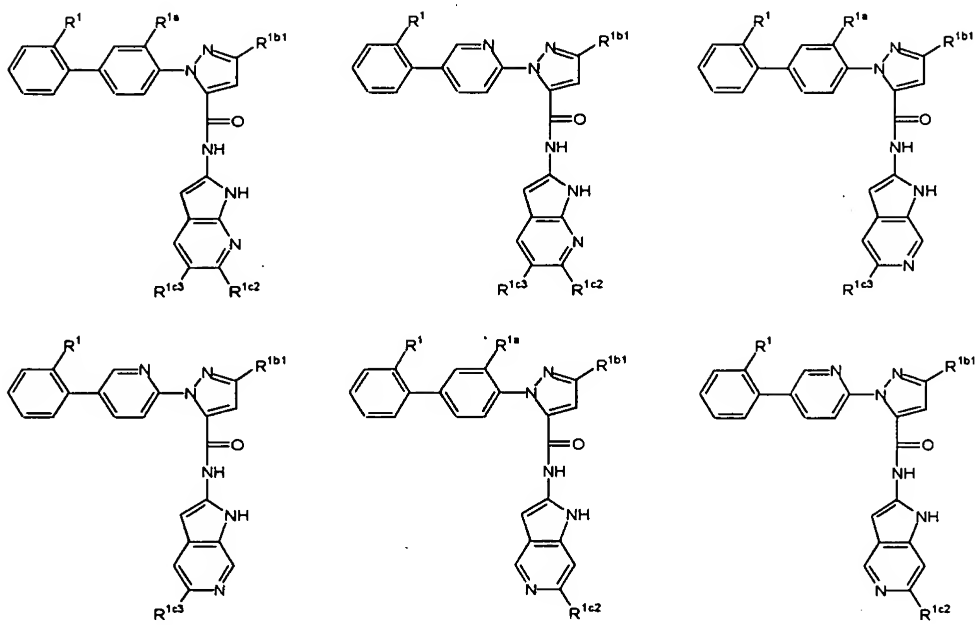
R^1 is selected from the group consisting of $-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and -OCH_3.

Table 51



wherein:

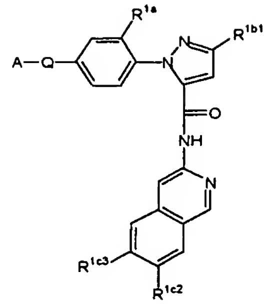
R^1 is selected from the group consisting of -SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

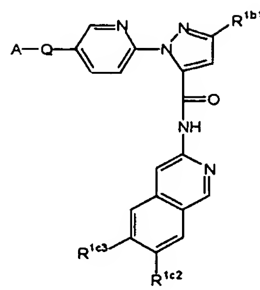
R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

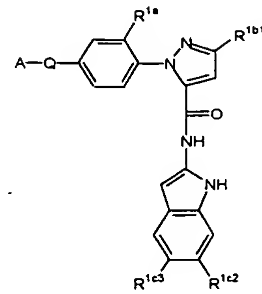
R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

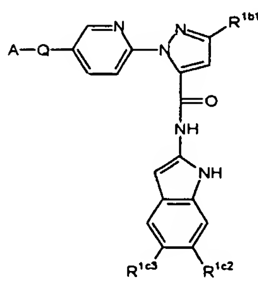
R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br, and -OCH_3.

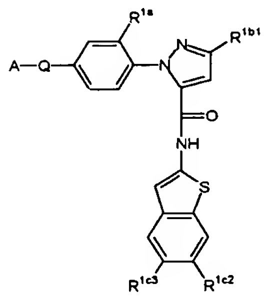
Table 52

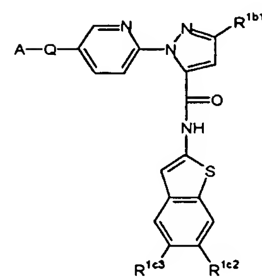


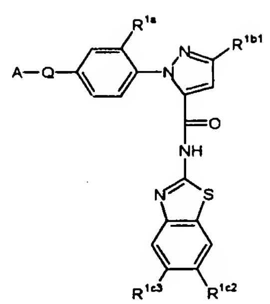


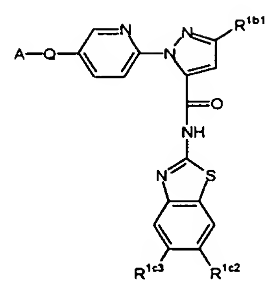






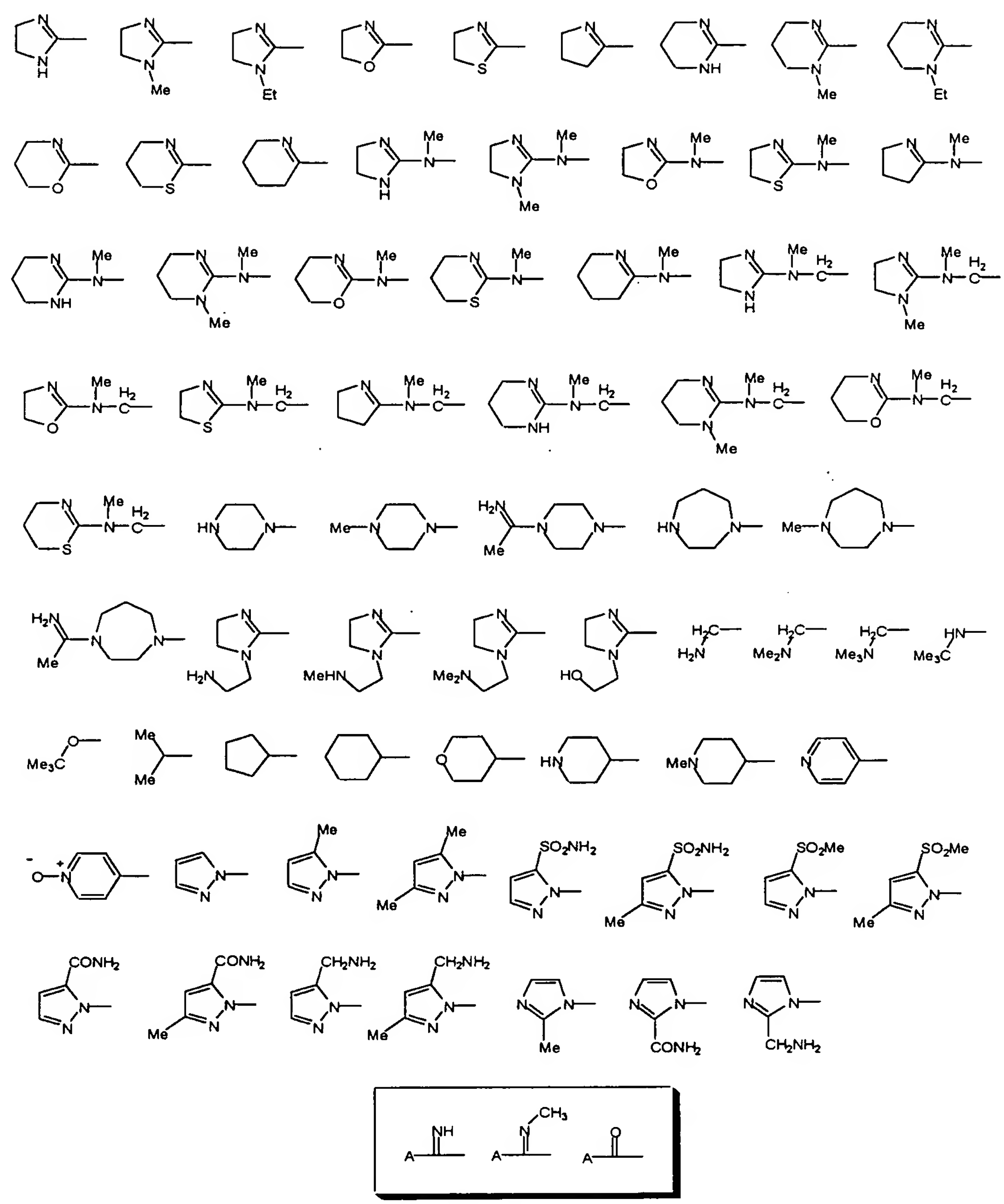






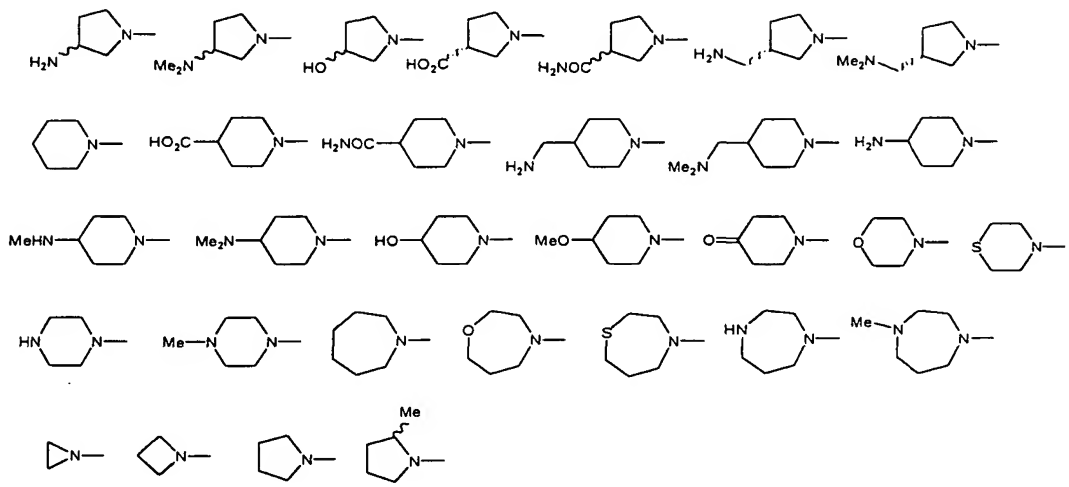
wherein:

A-Q is selected from the group consisting of:



wherein:

A is selected from the group consisting of:

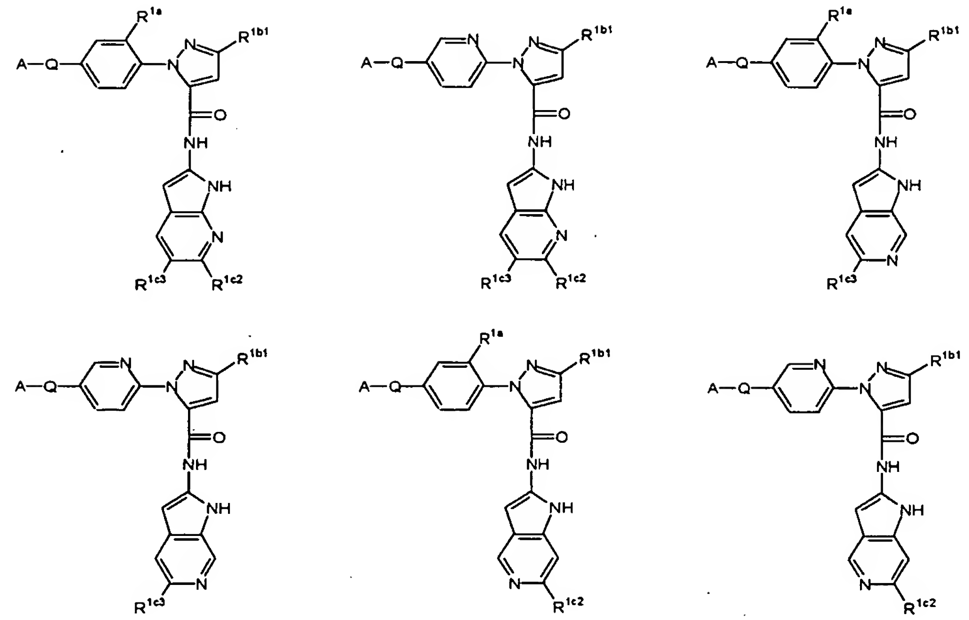


R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

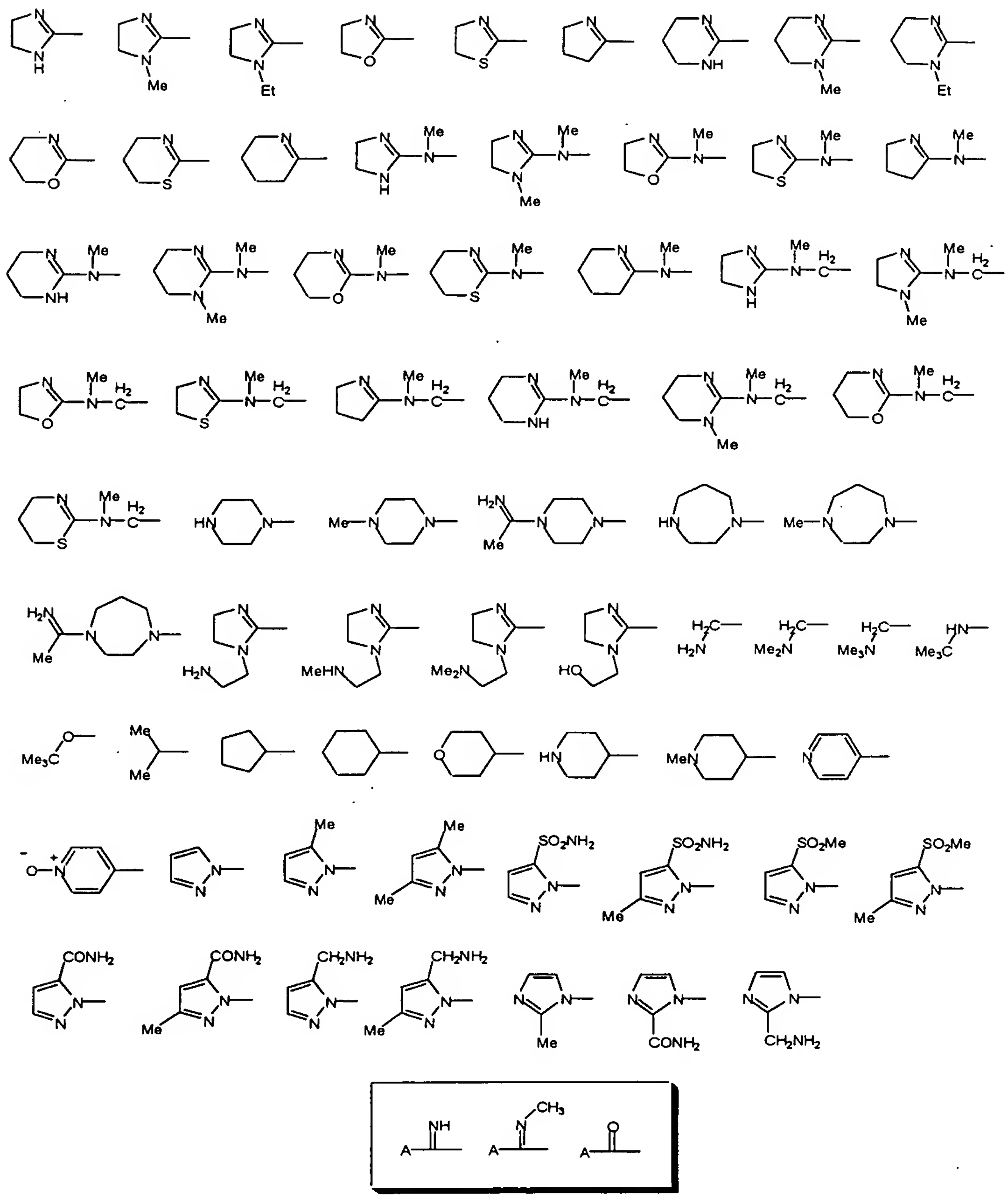
R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br and $-OCH_3$.

Table 53



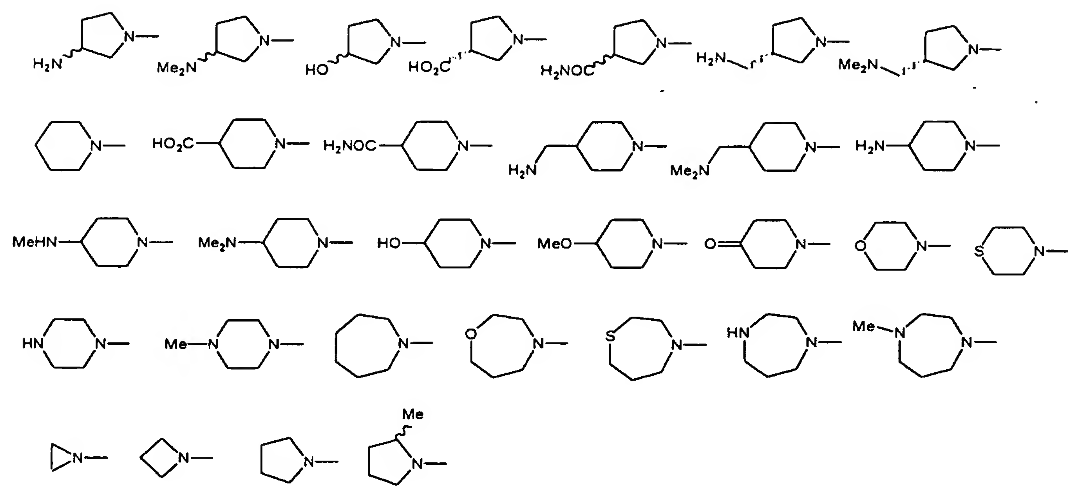
wherein:

A-Q is selected from the group consisting of:



wherein:

A is selected from the group consisting of:

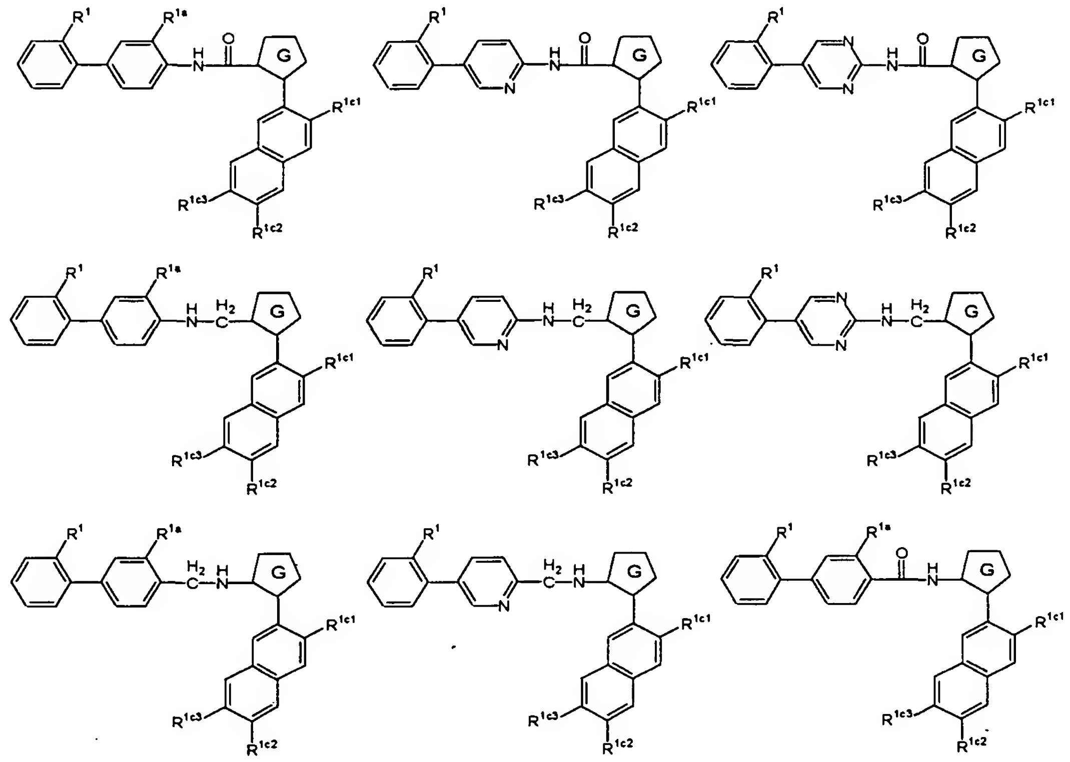


R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1c2} and R^{1c3} are independently selected from the group consisting of –H, -F, -Cl, -Br and $-OCH_3$.

The following compounds are an embodiment of the present invention:



wherein:

R^1 is selected from the group consisting of:

-SO_2NH_2, -SO_2Me, -CH_2NH_2 and -CH_2NMe_2;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, -NH_2, -OH, -SO_2Me, -SO_2Et, -SO_2NH_2, -NO_2, -CH_2NH_2, -CN, -$CONH_2$, -CH_2OH;

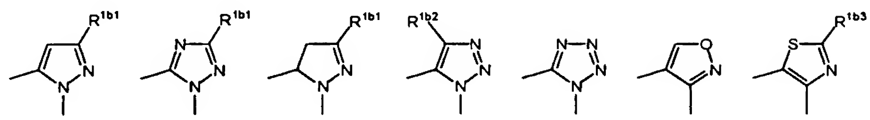
R^{1c2} is selected from the group consisting of:

-H, -F, -Cl and –Br;

R^{1c3} is selected from the group consisting of:

-H, -F, -Cl and –Br;

G is selected from the group consisting of:



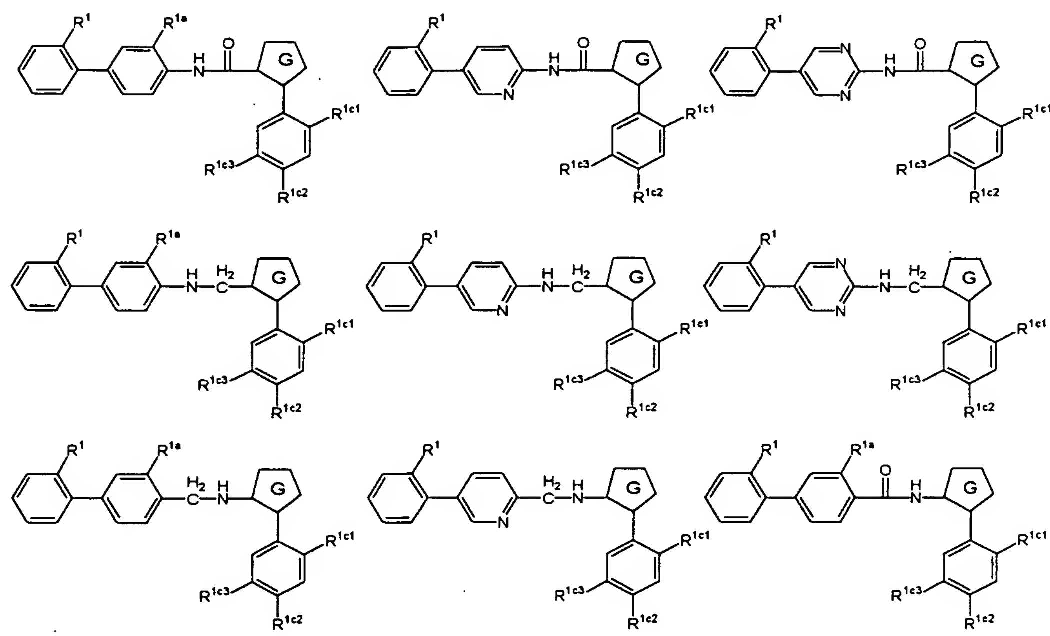
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

The following compounds are an embodiment of the present invention:



wherein :

R^1 is selected from the group consisting of:

$-SO_2NH_2$, $-SO_2Me$, $-CH_2NH_2$ and $-CH_2NMe_2$;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, $-NH_2$, -OH, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CH_2NH_2$, -CN, $-CONH_2$, $-CH_2OH$;

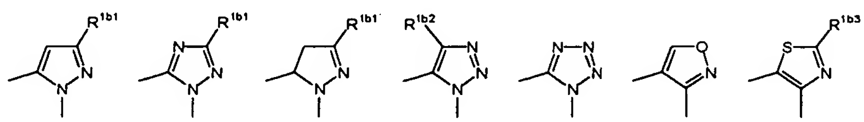
R^{1c2} is selected from the group consisting of:

-H, -F, -Cl, –Br and -OMe;

R^{1c3} is selected from the group consisting of:

-H, -F, -Cl, –Br, $-OCH_3$, $-NH_2$, $-CH_2NH_2$, $-CONH_2$, -CONHMe, $-CONMe_2$

G is selected from the group consisting of:



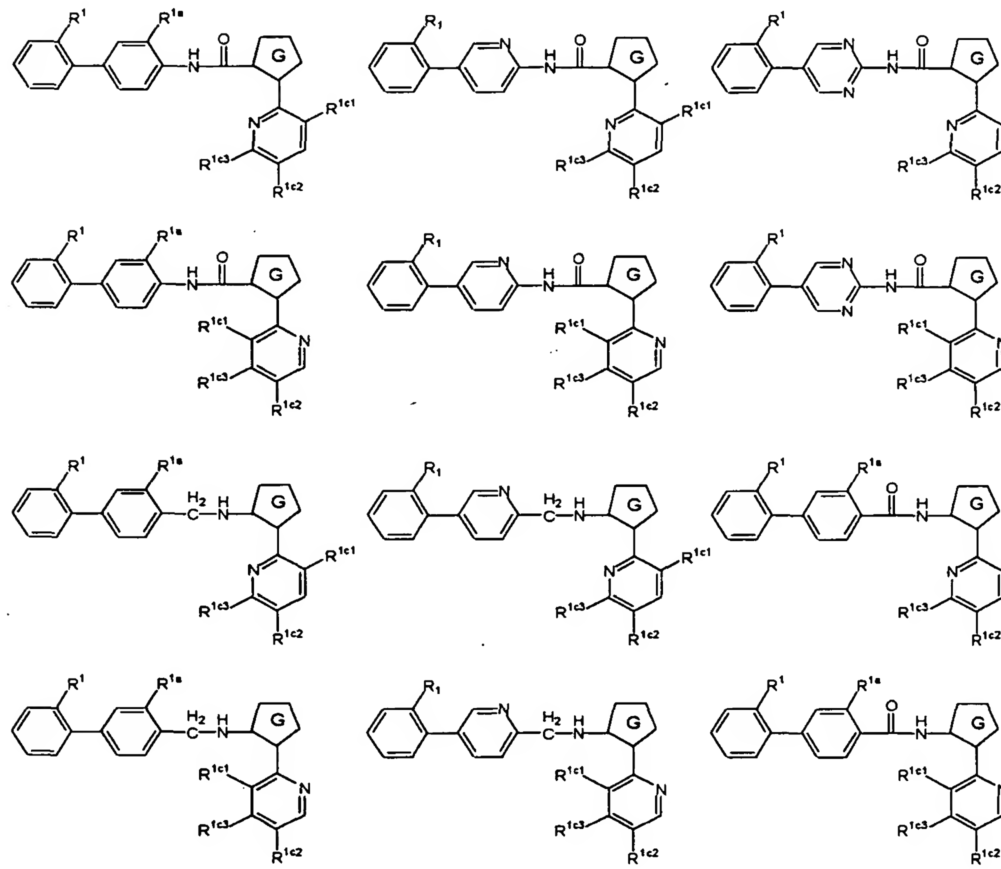
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

The following compounds are an embodiment of the present invention:



wherein:

R^1 is selected from the group consisting of:

$-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of:

–H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

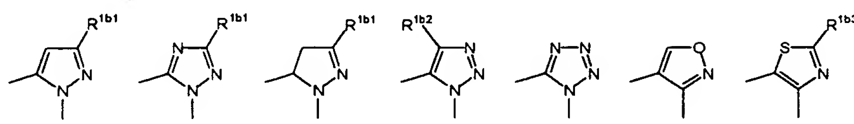
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of:

-H, -F, -Cl, –Br, $-OCH_3$, $-NH_2$, $-CH_2NH_2$, $-CONH_2$, -CONHMe, $-CONMe_2$;

G is selected from the group consisting of:



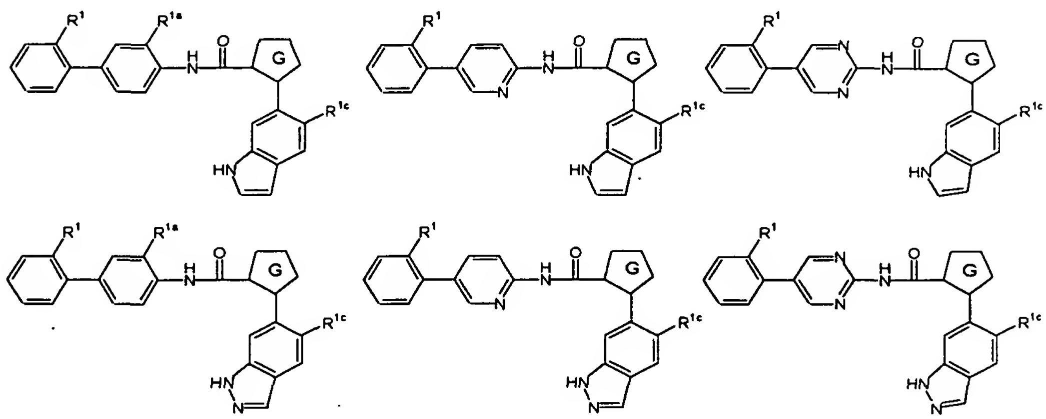
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

The following compounds are an embodiment of the present invention:



wherein:

R^1 is selected from the group consisting of:

-SO_2NH_2, -SO_2Me, -CH_2NH_2 and -CH_2NMe_2;

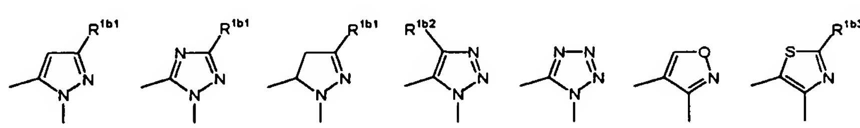
R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1c} is selected from the group consisting of:

-H, -F, -Cl, -Br, -NH_2, -OH, -SO_2Me, -SO_2Et, -SO_2NH_2, -NO_2, -CH_2NH_2, -CN, -$CONH_2$, -CH_2OH;

G is selected from the group consisting of:



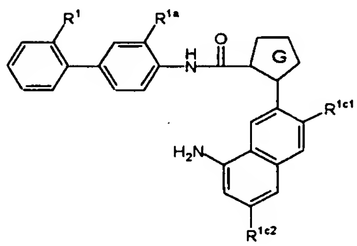
wherein:

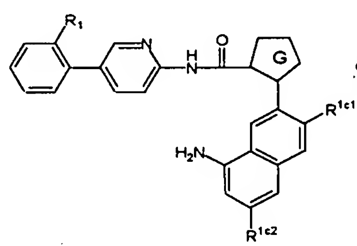
R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

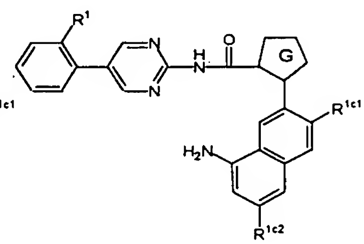
R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

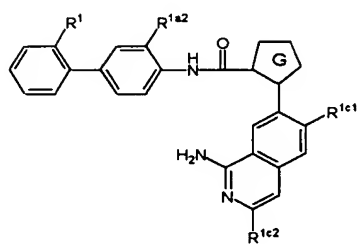
R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

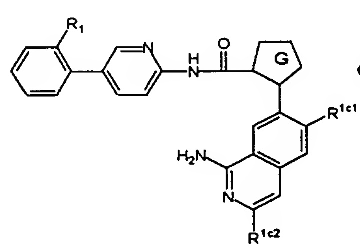
The following compounds are an embodiment of the present invention:

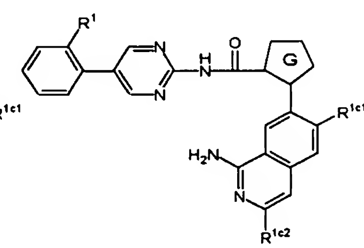












wherein:

R^1 is selected from the group consisting of:

-SO_2NH_2, -SO_2Me, -CH_2NH_2 and -CH_2NMe_2;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

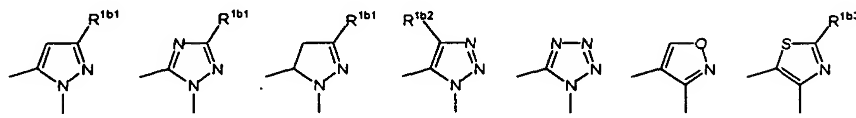
R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, $-NH_2$, -OH, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CH_2NH_2$, -CN, $-CONH_2$, $-CH_2OH$;

R^{1c2} is selected from the group consisting of:

-H, -F, -Cl and –Br;

G is selected from the group consisting of:



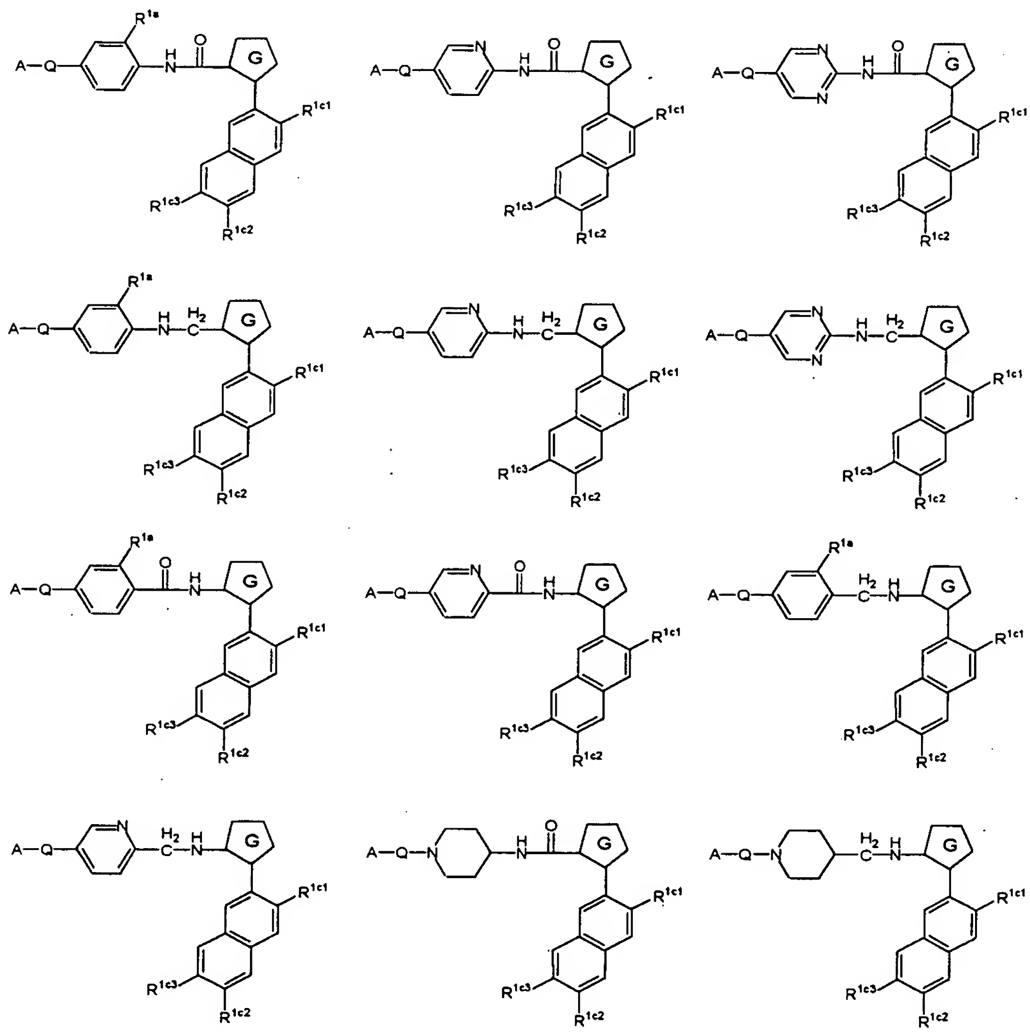
wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

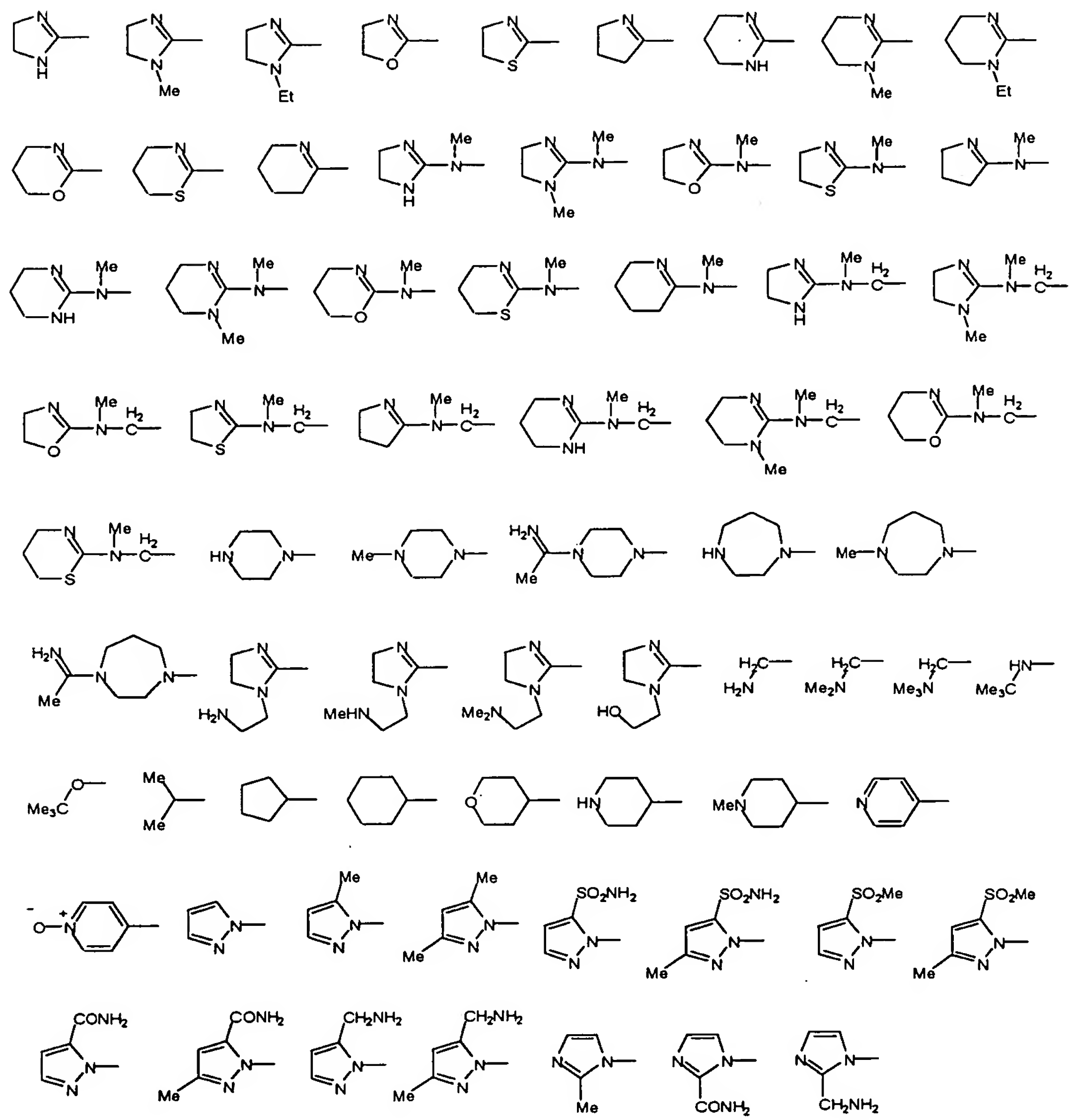
R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

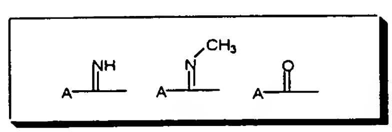
The following compounds are an embodiment of the present invention:



wherein:

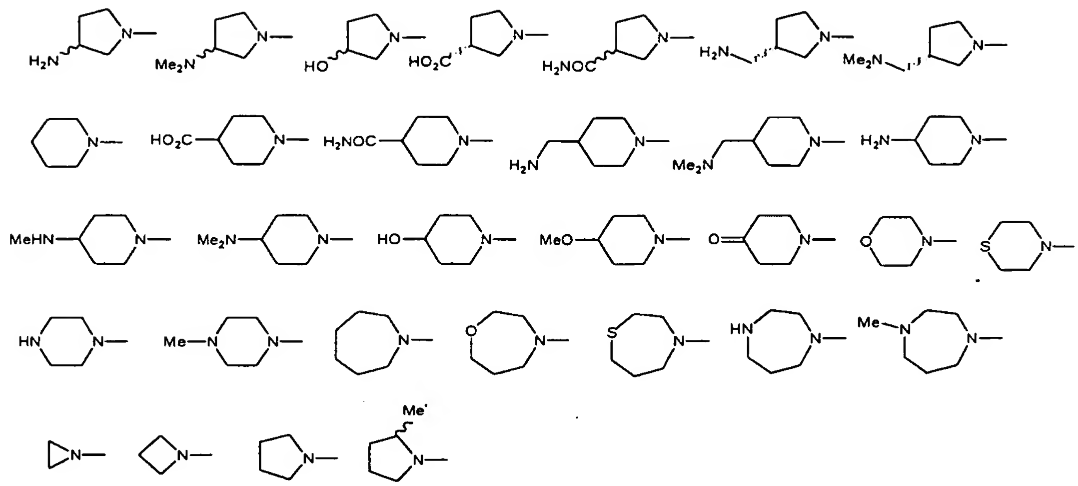
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of -H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, $-NH_2$, -OH, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CH_2NH_2$, -CN, $-CONH_2$, $-CH_2OH$;

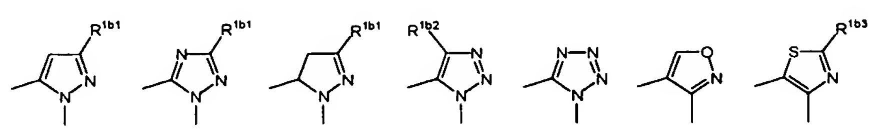
R^{1c2} is selected from the group consisting of:

-H, -F, -Cl and –Br;

R^{1c3} is selected from the group consisting of:

-H, -F, -Cl and –Br;

G is selected from the group consisting of:



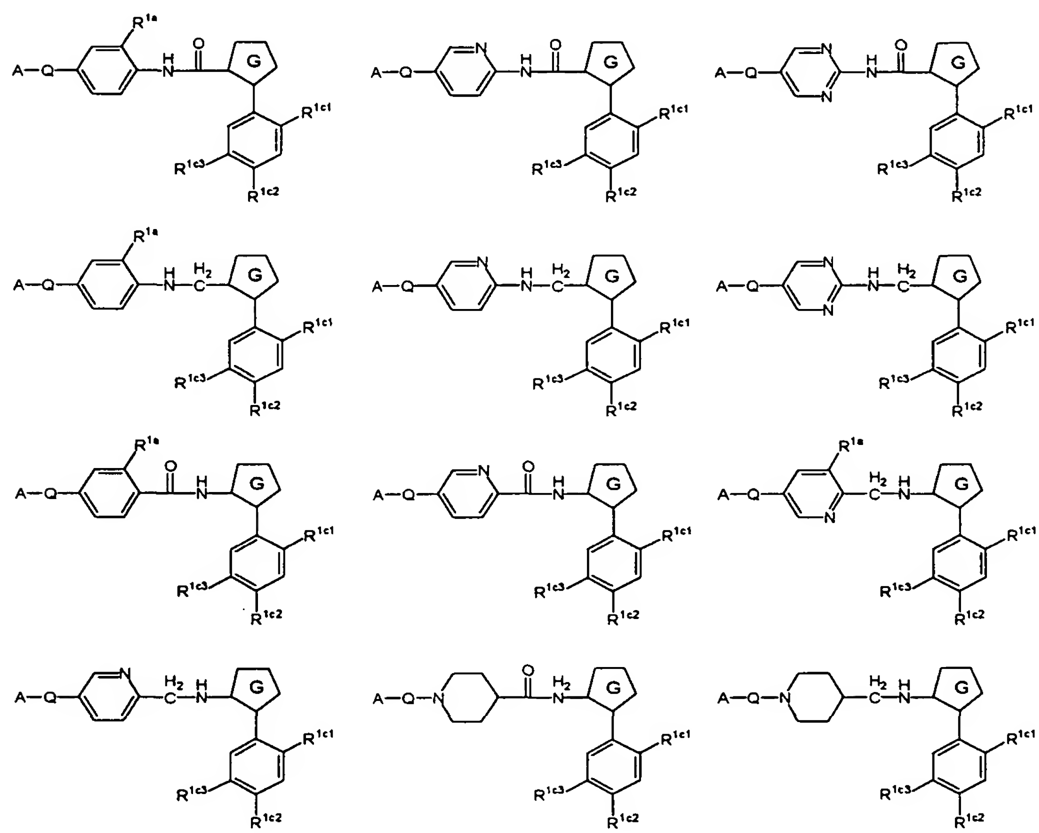
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

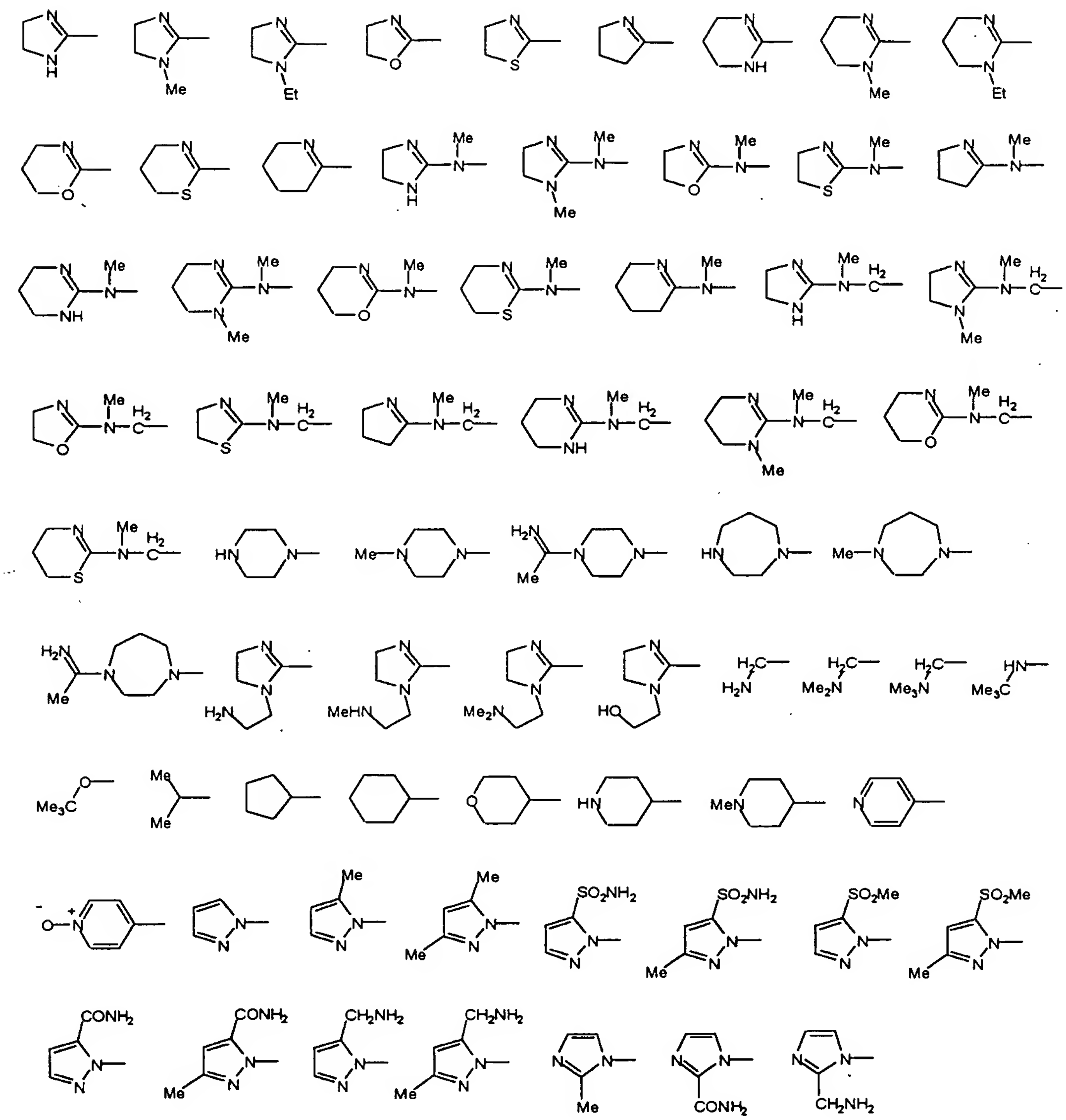
R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

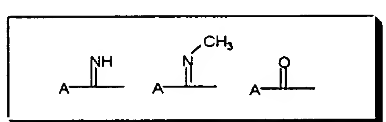
The following compounds are an embodiment of the present invention:



wherein:

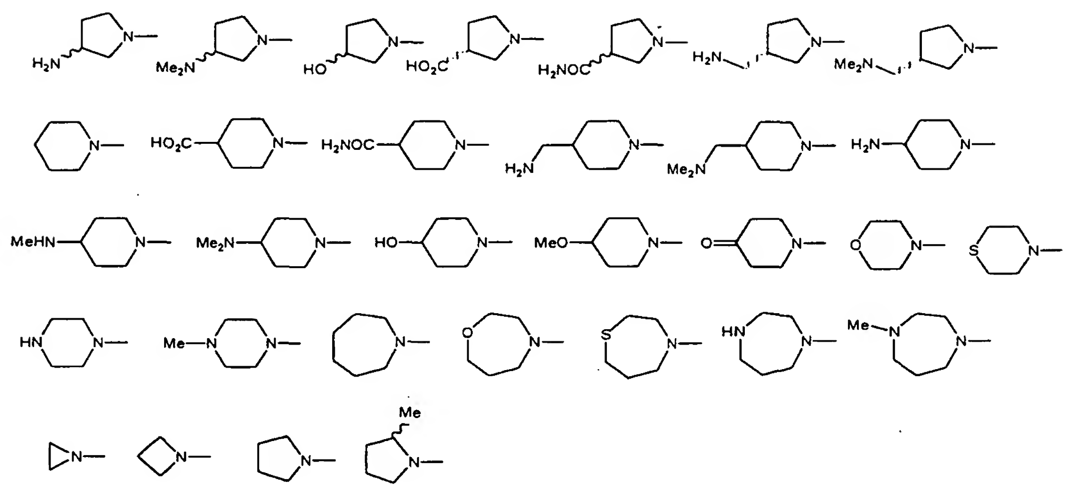
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of:

$-CH_3$, $-CF_3$, $-CH_2CH_3$, $-SO_2Me$, $-CONH_2$ and $-NHSO_2Me$;

R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, $-NH_2$, -OH, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CH_2NH_2$, -CN, $-CONH_2$, $-CH_2OH$;

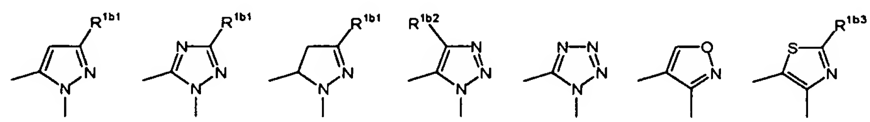
R^{1c2} is selected from the group consisting of:

-H, -F, -Cl, –Br and -OMe;

R^{1c3} is selected from the group consisting of:

–H, -F, -Cl, -Br, -OH, $-OCH_3$, $-NH_2$, $-CONH_2$, $-CH_2NH_2$;

G is selected from the group consisting of:



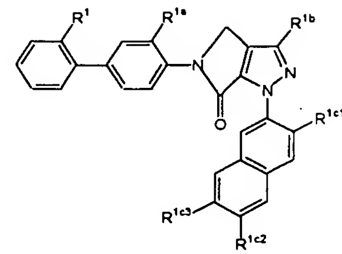
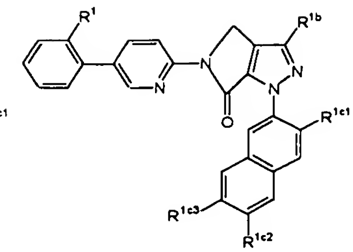
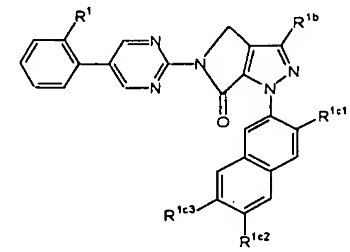
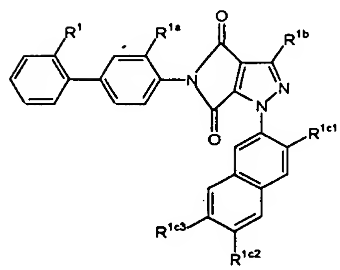
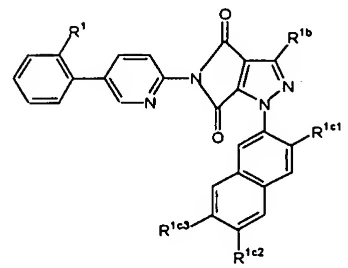
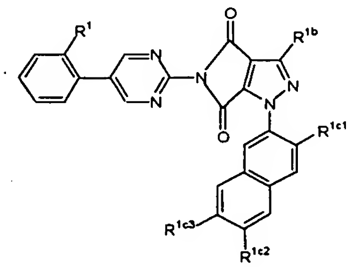
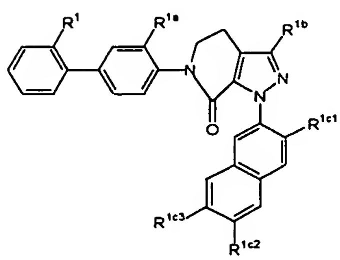
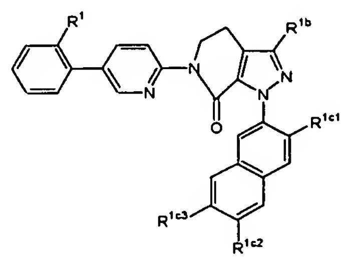
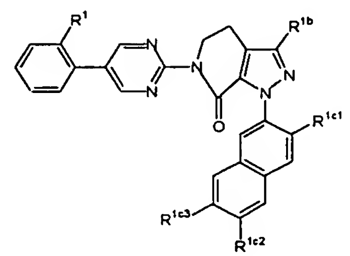
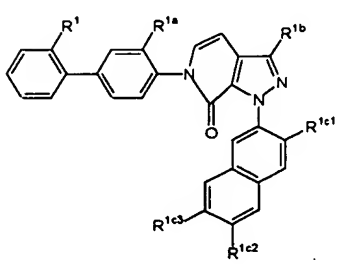
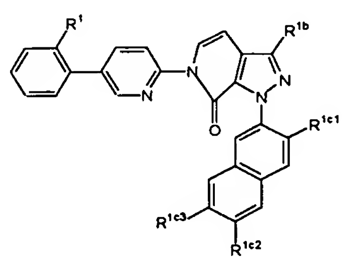
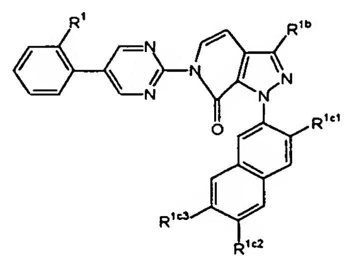
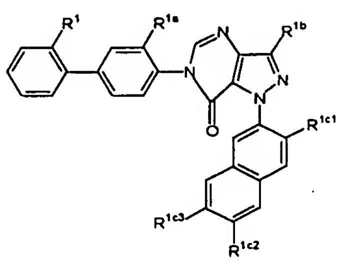
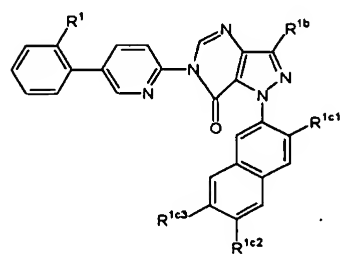
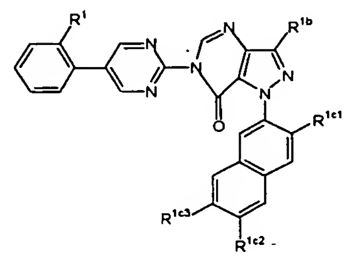
wherein:

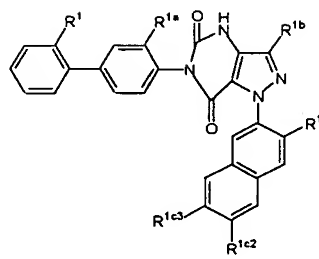
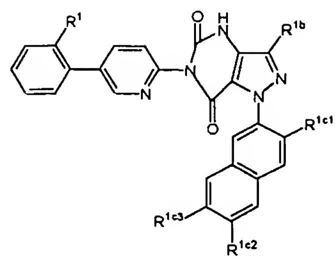
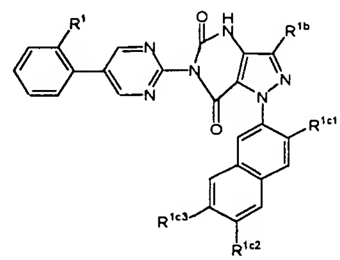
R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

The following compounds are an embodiment of the present invention:

wherein:

R^1 is selected from the group consisting of:

-SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -CONH(CH_3), -CON$(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of:

–H, -F, -Cl and Br;

R^{1b} is selected from the group consisting of:

–CH_3 and -CF_3;

R^{1c1} is selected from the group consisting of:

–H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

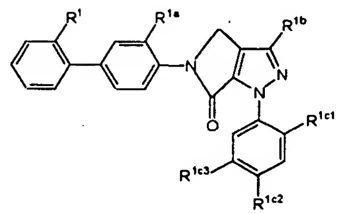
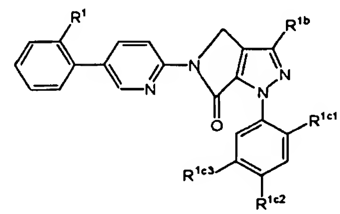
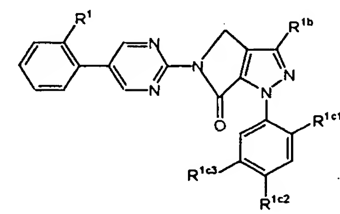
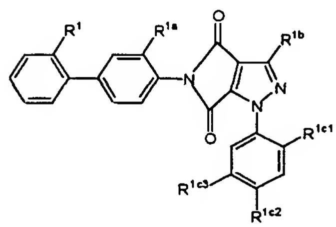
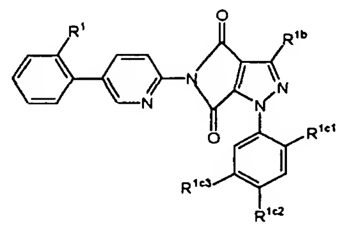
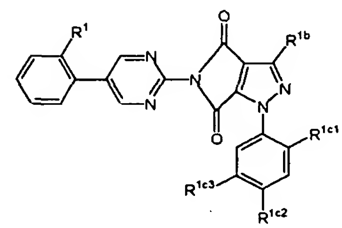
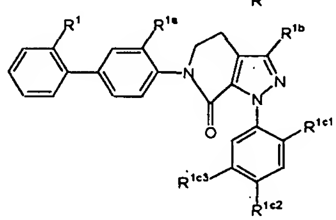
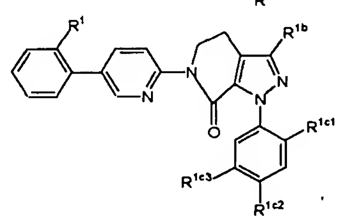
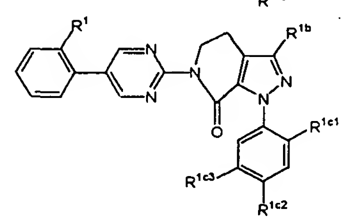
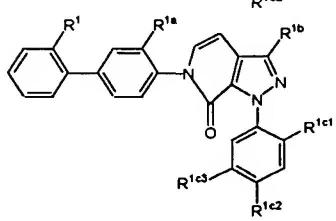
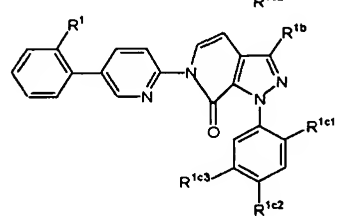
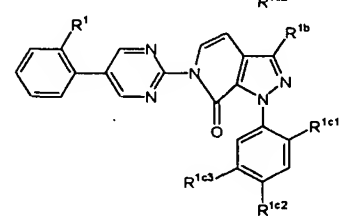
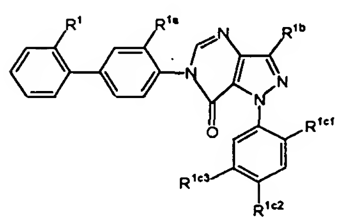
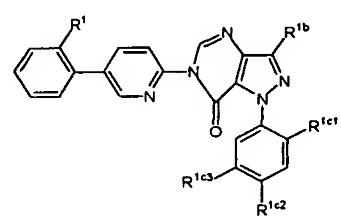
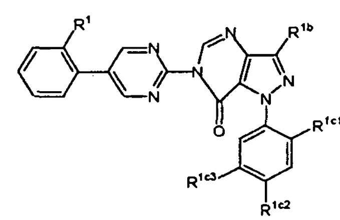
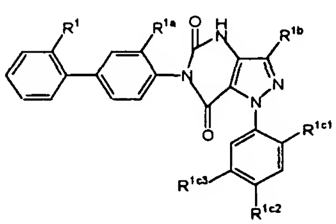
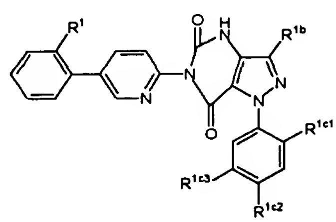
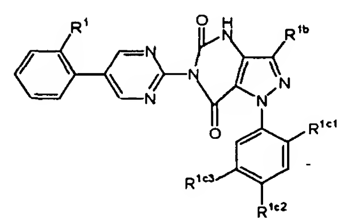
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl and -Br;

R^{1c3} is selected from the group consisting of:

–H, -F, -Cl and -Br.

The following compounds are an embodiment of the present invention:

wherein:

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of:

$-CH_3$, $-CF_3$, $-CH_2CH_3$, $-SO_2Me$, $-CONH_2$ and $-NHSO_2Me$;

R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, $-NH_2$, -OH, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CH_2NH_2$, -CN, $-CONH_2$, $-CH_2OH$;

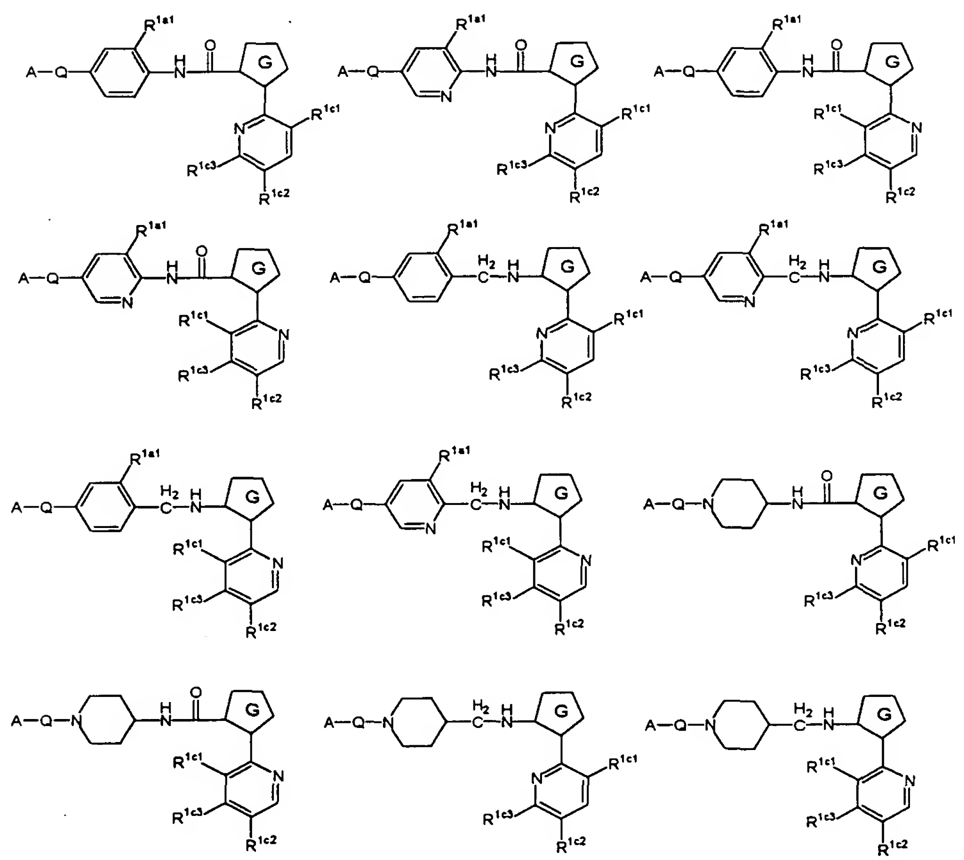
R^{1c2} is selected from the group consisting of:

-H, -F, -Cl, –Br and $–OCH_3$;

R^{1c3} is selected from the group consisting of:

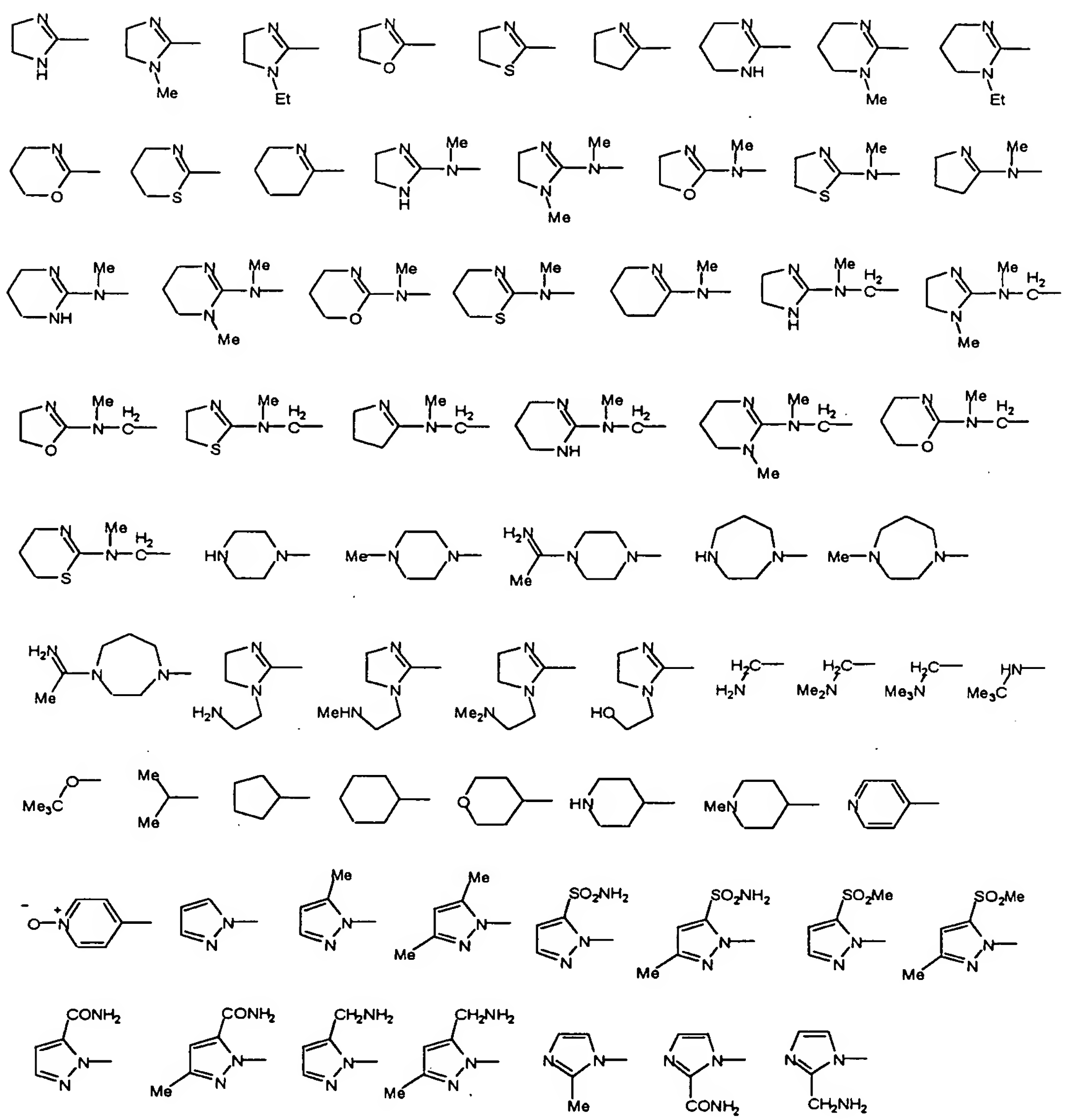
-H, -F, -Cl, –Br, $-OCH_3$, $-NH_2$, $-CH_2NH_2$, $-CONH_2$, -CONHMe, $-CONMe_2$.

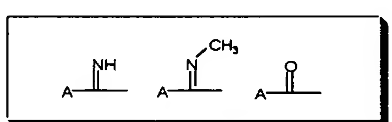
The following compounds are an embodiment of the present invention:



wherein:

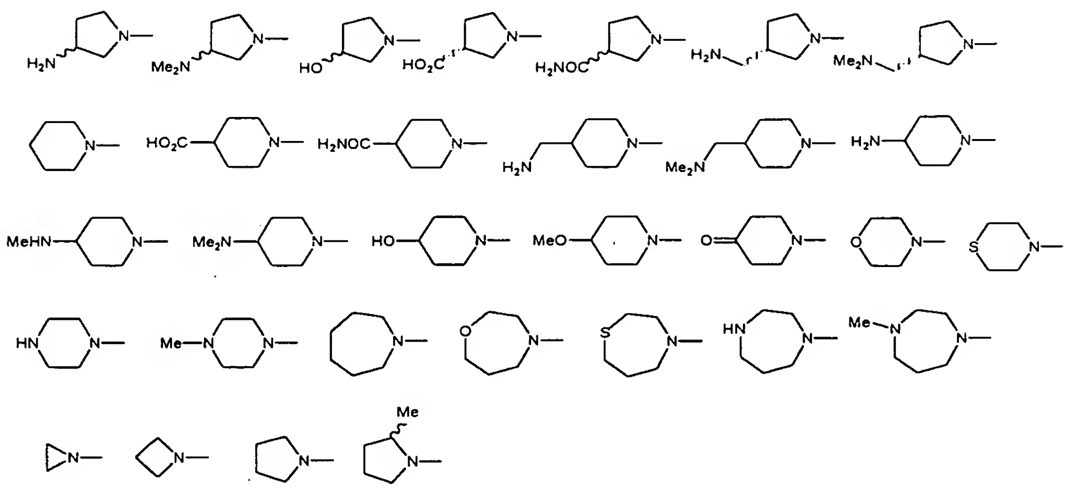
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1c1} is selected from the group consisting of:

–H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

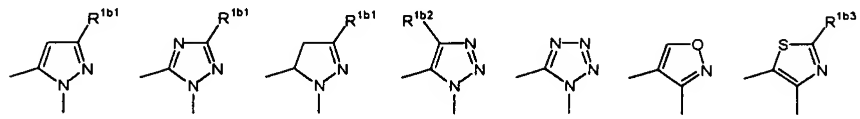
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl, -Br, and $-OCH_3$;

R^{1c3} is selected from the group consisting of:

-H, -F, -Cl, –Br, $-OCH_3$, $-NH_2$, $-CH_2NH_2$, $-CONH_2$, -CONHMe, $-CONMe_2$;

G is selected from the group consisting of:



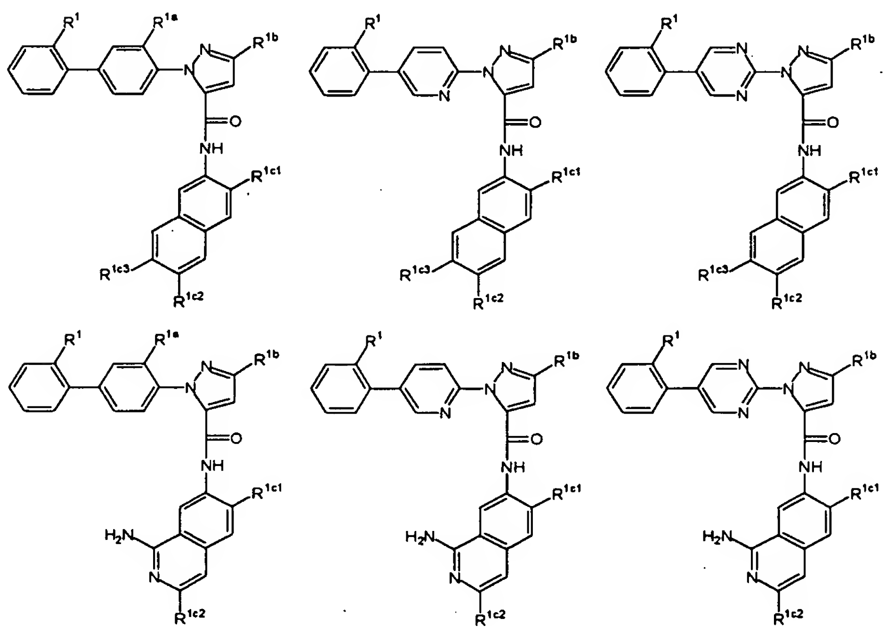
wherein:

R^{1b1} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b2} is selected from the group consisting of –H, -CH_3 and –CF_3;

R^{1b3} is selected from the group consisting of –Cl, -NH_2, -CH_3 and –CF_3.

The following compounds are an embodiment of the present invention:



wherein:

R^1 is selected from the group consisting of:

-SO_2NH_2, -SO_2CH_3, –CN, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -CH_2NH_2, -$CH_2NH(CH_3)$, -$CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of:

–H, -CH_3 and –CF_3;

R^{1c1} is selected from the group consisting of:

–H, –F, -Cl, -Br, -CN, -CH_2NH_2, -CH_2OH, -$CONH_2$, -C(=NH)NH_2, -CO_2H, -CO_2Me, -SO_2Me, -SO_2NH_2, -OH, -NH_2, and -NO_2;

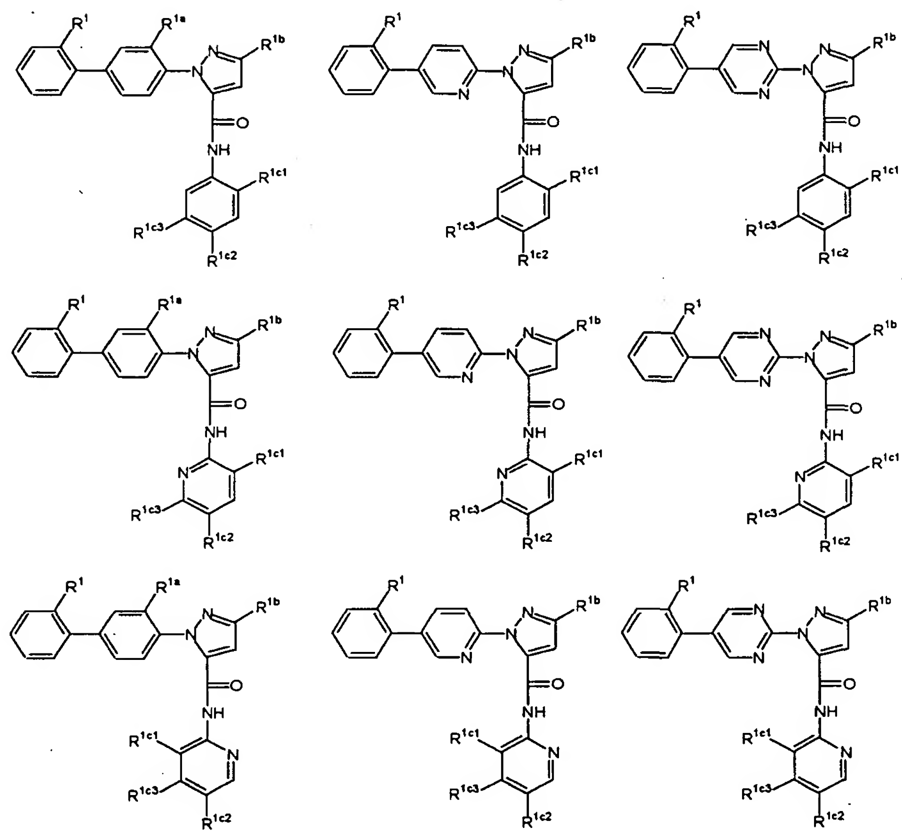
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl and -Br;

R^{1c3} is selected from the group consisting of:

–H, -F, -Cl and –Br.

The following compounds are an embodiment of the present invention:



wherein:

R^1 is selected from the group consisting of:

$-SO_2NH_2$, $-SO_2CH_3$, $-CN$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CH_2NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of:

–H, -CH_3 and –CF_3;

R^{1c1} is selected from the group consisting of:

–H, –F, -CN, -CH_2NH_2, -$CONH_2$, -SO_2Me, -SO_2NH_2 and -NO_2;

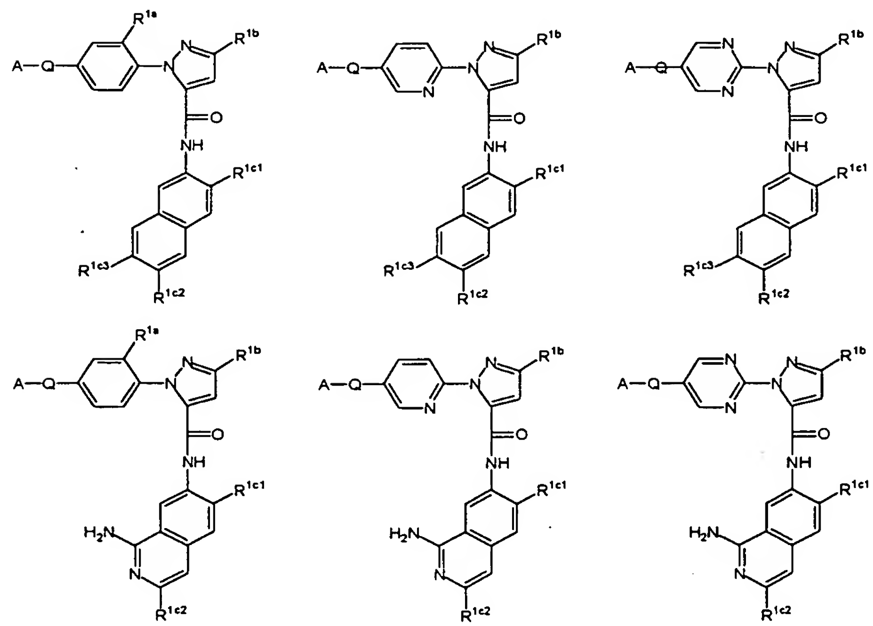
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl, -Br and –OCH_3;

R^{1c3} is selected from the group consisting of:

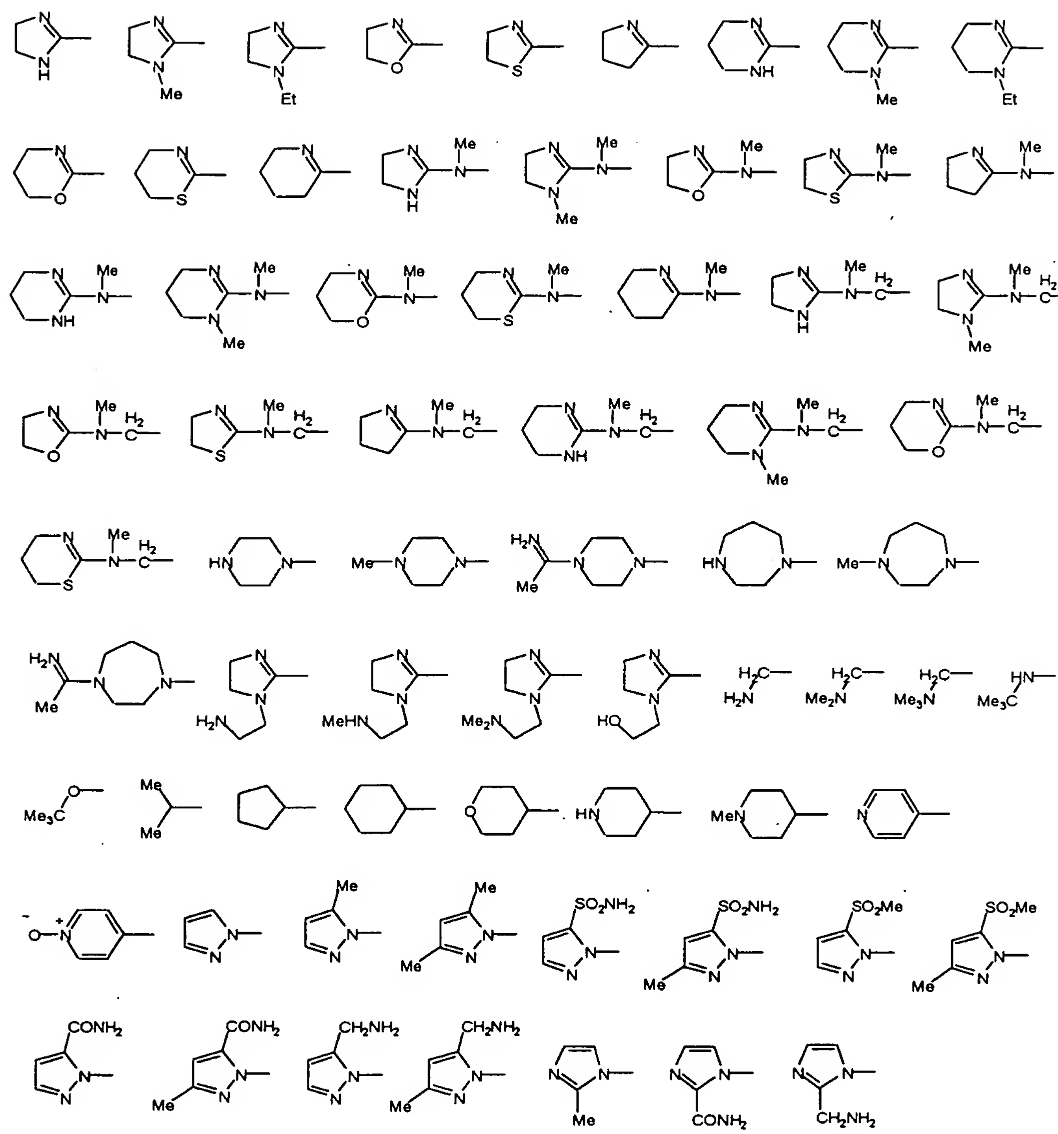
-H, -F, -Cl, –Br, -OCH_3, -NH_2, -CH_2NH_2, -$CONH_2$, -CONHMe, -$CONMe_2$.

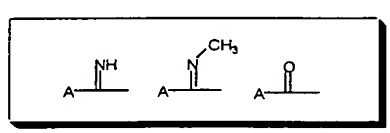
The following compounds are an embodiment of the present invention:



wherein:

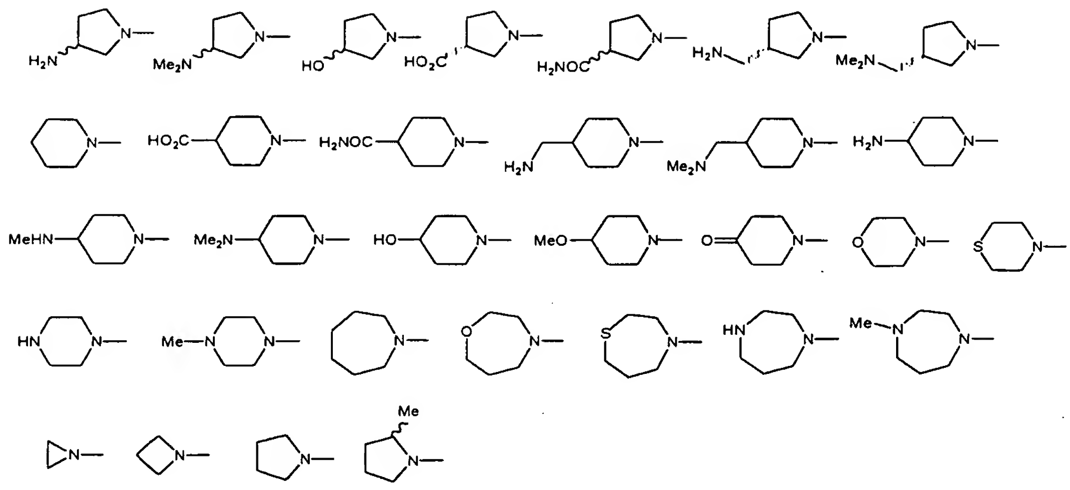
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of:

–H, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of:

–H, –F, -Cl, -Br, -CN, $-CH_2NH_2$, $-CH_2OH$, $-CONH_2$, $-C(=NH)NH_2$, $-CO_2H$, $-CO_2Me$, $-SO_2Me$, $-SO_2NH_2$, -OH, $-NH_2$, and $-NO_2$;

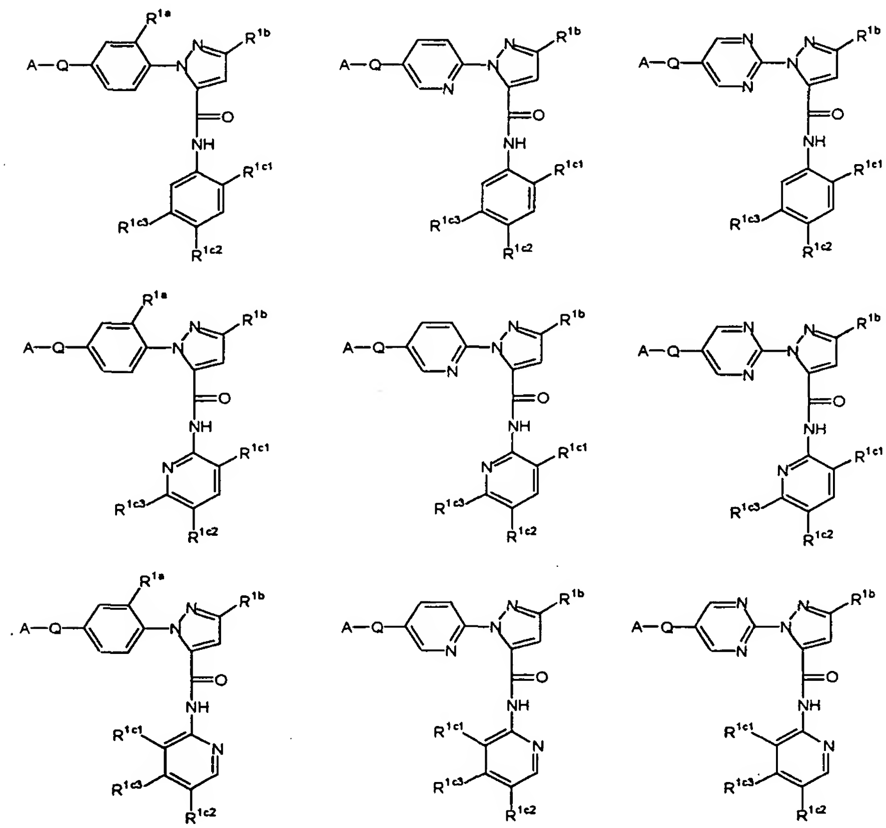
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl and -Br;

R^{1c3} is selected from the group consisting of:

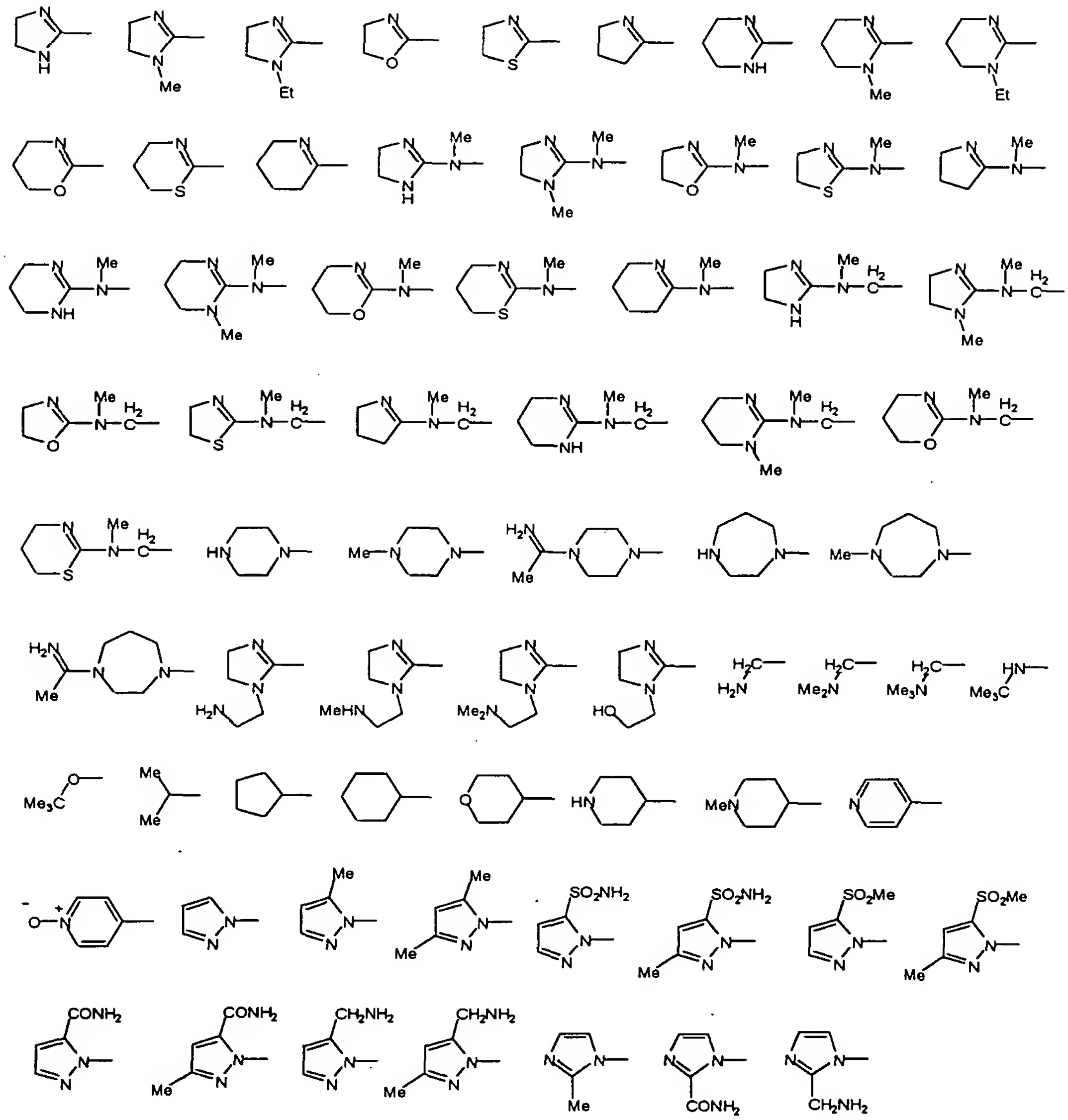
–H, -F, -Cl and –Br.

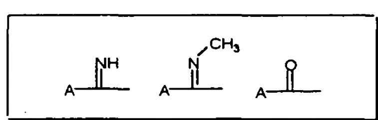
The following compounds are an embodiment of the present invention:



wherein:

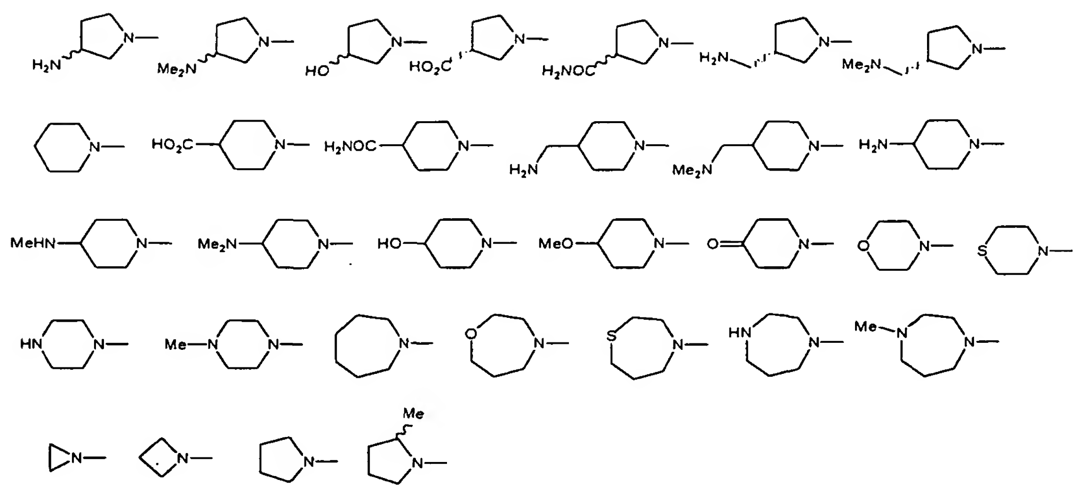
A-Q is selected from the group consisting of:





wherein:

A is selected from the group consisting of:



R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

R^{1b} is selected from the group consisting of:

–H, $-CH_3$ and $-CF_3$;

R^{1c1} is selected from the group consisting of:

–H, –F, -CN, $-CH_2NH_2$, $-CONH_2$, $-SO_2Me$, $-SO_2NH_2$ and $-NO_2$;

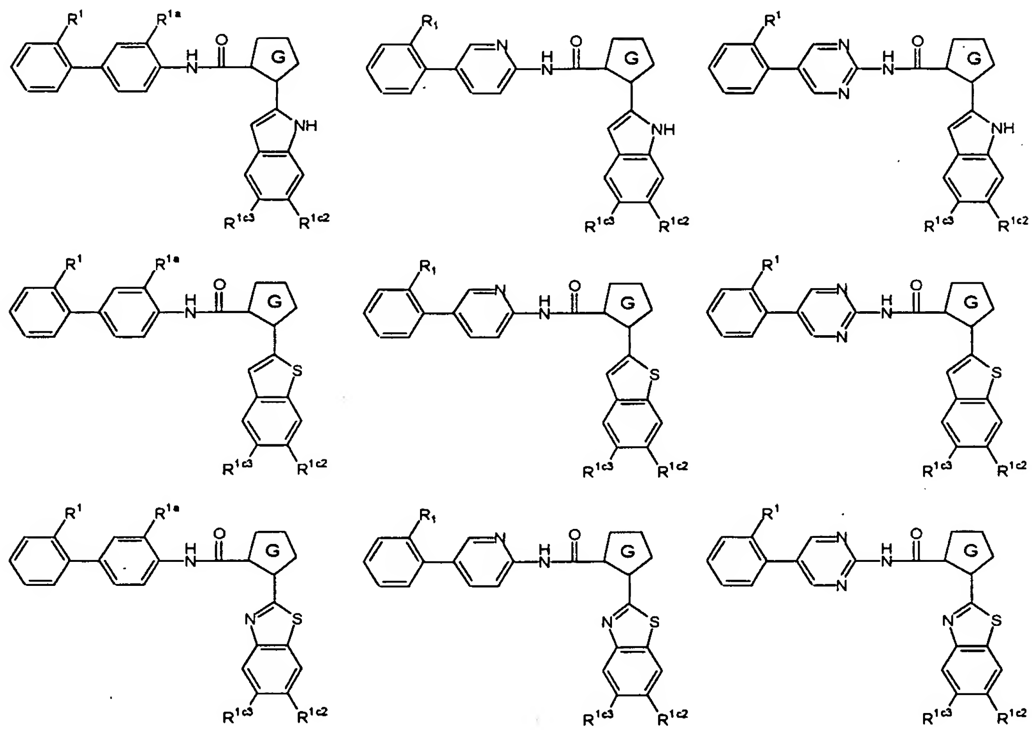
R^{1c2} is selected from the group consisting of:

–H, -F, -Cl, -Br and $-OCH_3$;

R^{1c3} is selected from the group consisting of:

-H, -F, -Cl, –Br, $-OCH_3$, $-NH_2$, $-CH_2NH_2$, $-CONH_2$, -CONHMe, $-CONMe_2$.

The following compounds are an embodiment of the present invention:



Wherein:

R^1 is selected from the group consisting of:

$-SO_2NH_2$, $-SO_2Me$, $-CH_2NH_2$ and $-CH_2NMe_2$;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

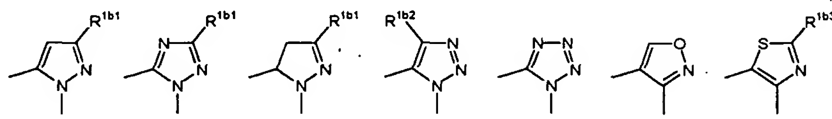
R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, $-NH_2$, -OH, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CH_2NH_2$, -CN, $-CONH_2$, $-CH_2OH$;

R^{1c2} and R^{1c3} are independently selected from the group consisting of:

-H, -F, -Cl and –Br;

G is selected from the group consisting of:



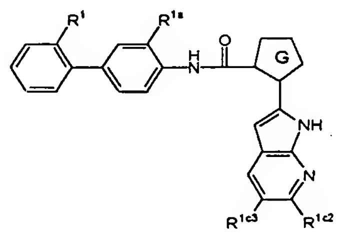
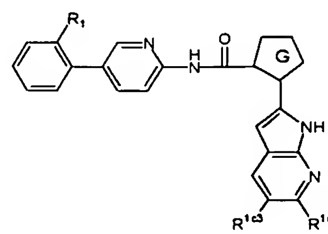
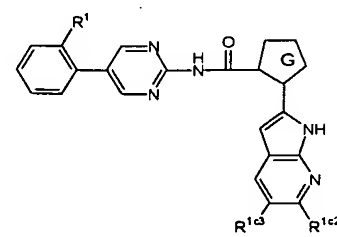
wherein:

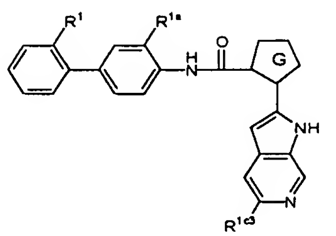
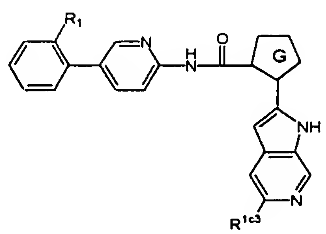
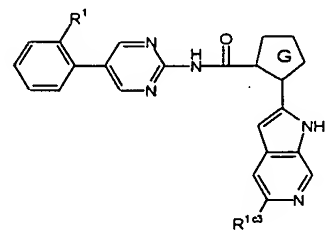
R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $–CF_3$;

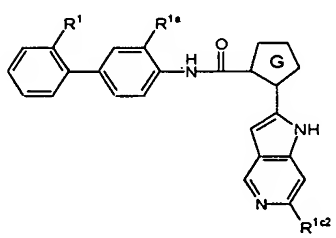
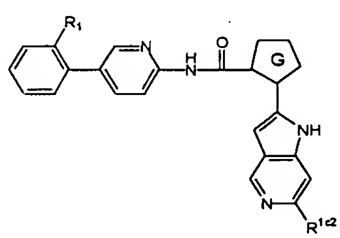
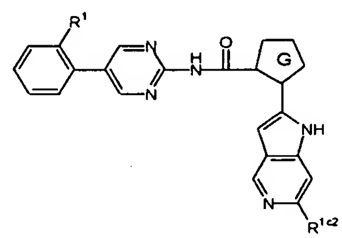
R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $–CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $–CF_3$.

The following compounds are an embodiment of the present invention:

wherein:

R^1 is selected from the group consisting of:

-SO_2NH_2, -SO_2Me, -CH_2NH_2 and -CH_2NMe_2;

R^{1a} is selected from the group consisting of:

-H, -F, -Cl and -Br;

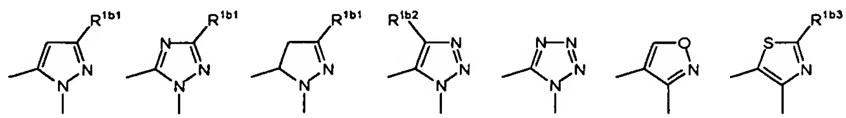
R^{1c1} is selected from the group consisting of:

-H, -F, -Cl, -Br, -NH_2, -OH, -SO_2Me, -SO_2Et, -SO_2NH_2, -NO_2, -CH_2NH_2, -CN, -$CONH_2$, -CH_2OH;

R^{1c2} and R^{1c3} are independently selected from the group consisting of:

-H, -F, -Cl and –Br;

G is selected from the group consisting of:



wherein:

R^{1b1} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b2} is selected from the group consisting of –H, $-CH_3$ and $-CF_3$;

R^{1b3} is selected from the group consisting of –Cl, $-NH_2$, $-CH_3$ and $-CF_3$.

This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates and solvates of the compounds of the formula (I). In addition, the compounds of formula (I) can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Preparation of Compounds

The compounds of the present invention may be synthesized by standard organic chemical synthetic methods as described and referenced in standard textbooks. These methods are well known in the art. See, e.g., March, "Advanced Organic Chemistry", John Wiley & Sons, New York,, 1992; Joule, Mills and Smith, “Heterocyclic Chemistry”, Chapman & Hall, London, 1995, et seq.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Fluka, Lancaster, TCI, Maybridge, Frontier, Fluorochem, Alfa Aesar, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the syntheses of these compounds, the functional groups of the substitutents are optionally protected by blocking groups to prevent cross reaction. Examples of suitable protective groups and their use are described in Kocienski, "Protecting Groups", Thieme, Stuttgart, 1994; Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1999, and the disclosures of which are incorporated herein by reference.

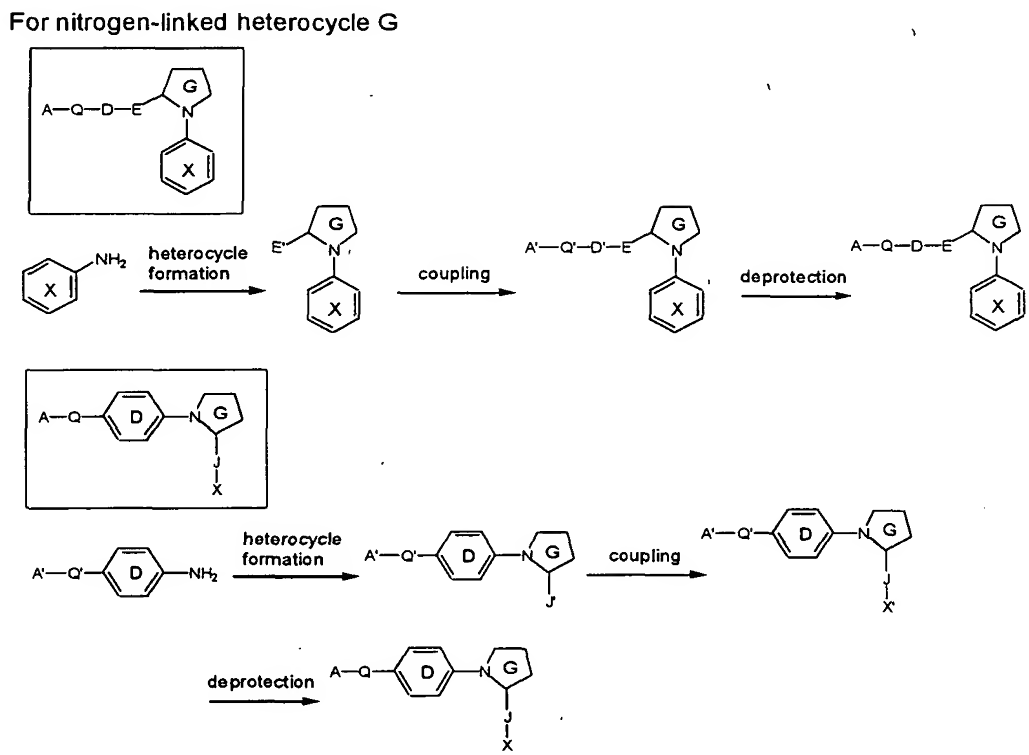
Non-limiting exemplary synthesis schemes are outlined directly below, and specific steps are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by flash column chromatography, reverse-phase preparative high performance liquid chromatography (HPLC) with high purity water and acetonitrile, or other appropriate methods.

General Synthesis

General synthesis for compounds with a N-linked G ring is outlined in Scheme 1. A', Q', D', E', J' and X' are protected functional structures which can be converted to A, Q, D, E, J and X respectively. For formation of the N-linked G ring, the appropriate aromatic amine precursor is treated under conditions described in Joule, Mills and Smith, "Heterocyclic Chemistry", Chapman & Hall, London, 1995, or the

references cited therein, or as described later in the preparation section to give the G ring.

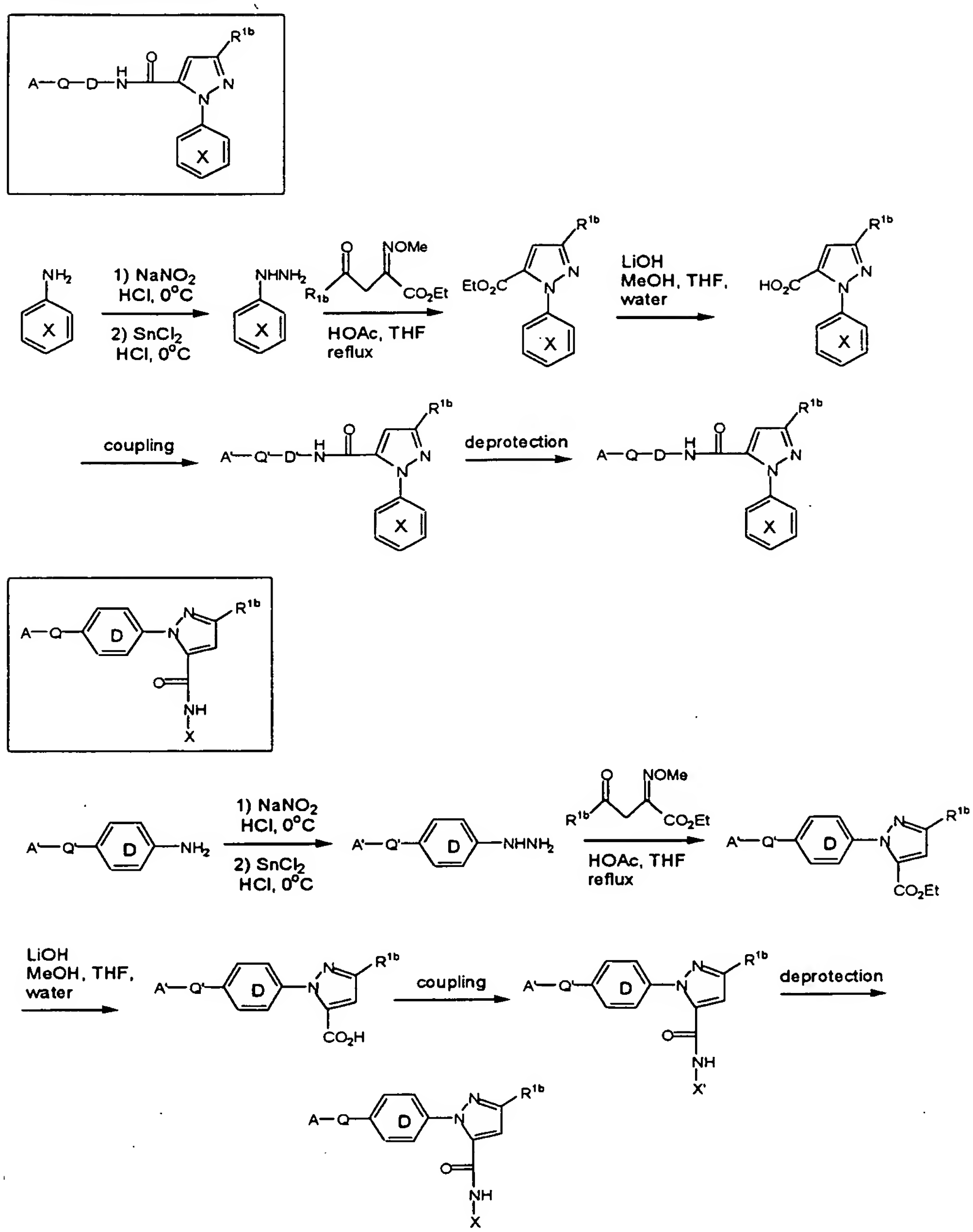
Scheme 1



Scheme 2 shows the general synthesis of compounds with a N-linked pyrazole G ring. Appropriately protected aromatic amines are converted to aromatic hydrazines by reduction of their diazonium salts. The hydrazines are condensed with 1,3-diketones to yield the pyrazole structures.

Scheme 2

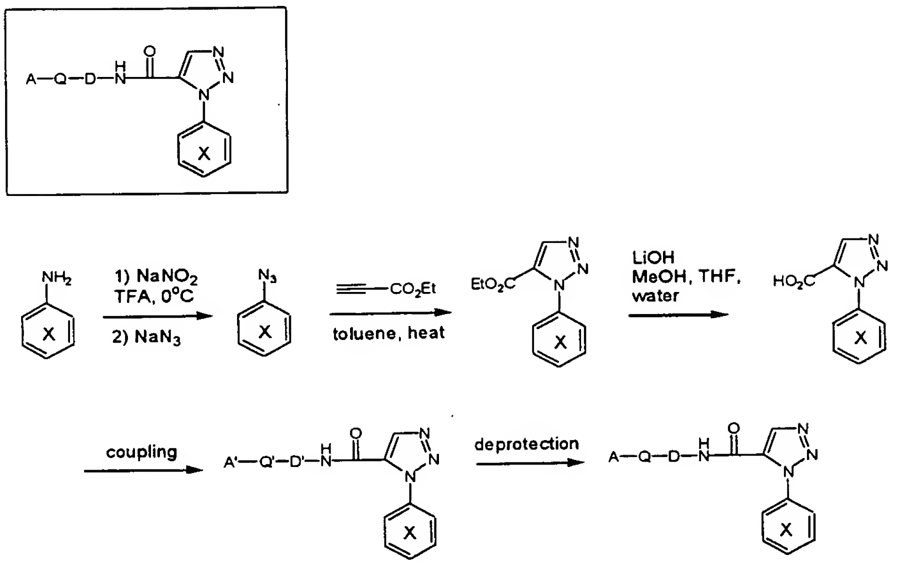
For pyrazole-linked compounds

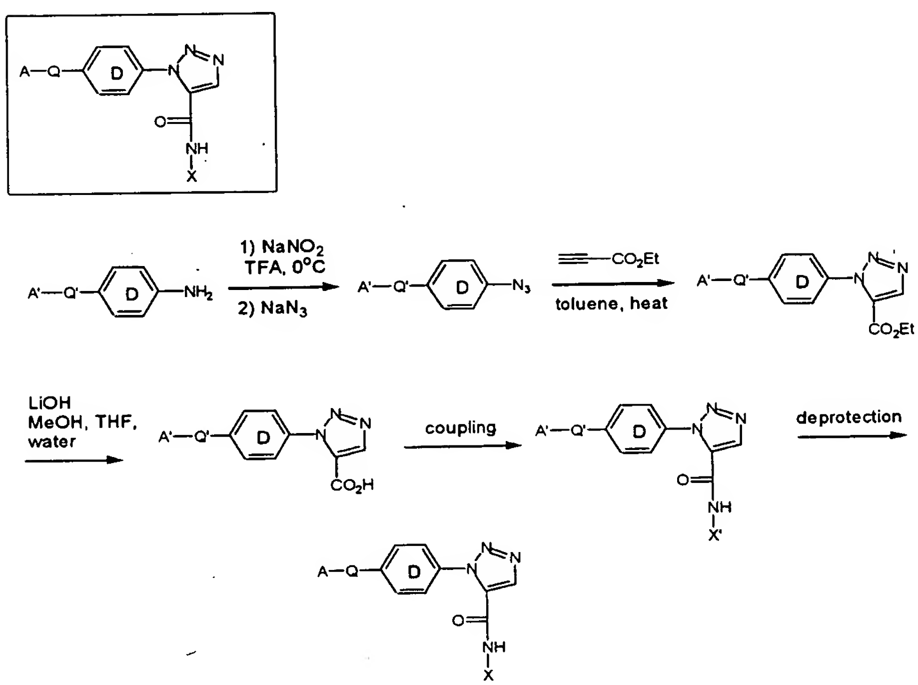


Scheme 3 shows the general synthesis of compounds with a N-linked triazole G ring. An appropriately protected aromatic amine is converted to aromatic azide from its diazonium salt. The azide is condensed with an alkyne to yield the triazole structure.

Scheme 3

For triazole-linked compounds

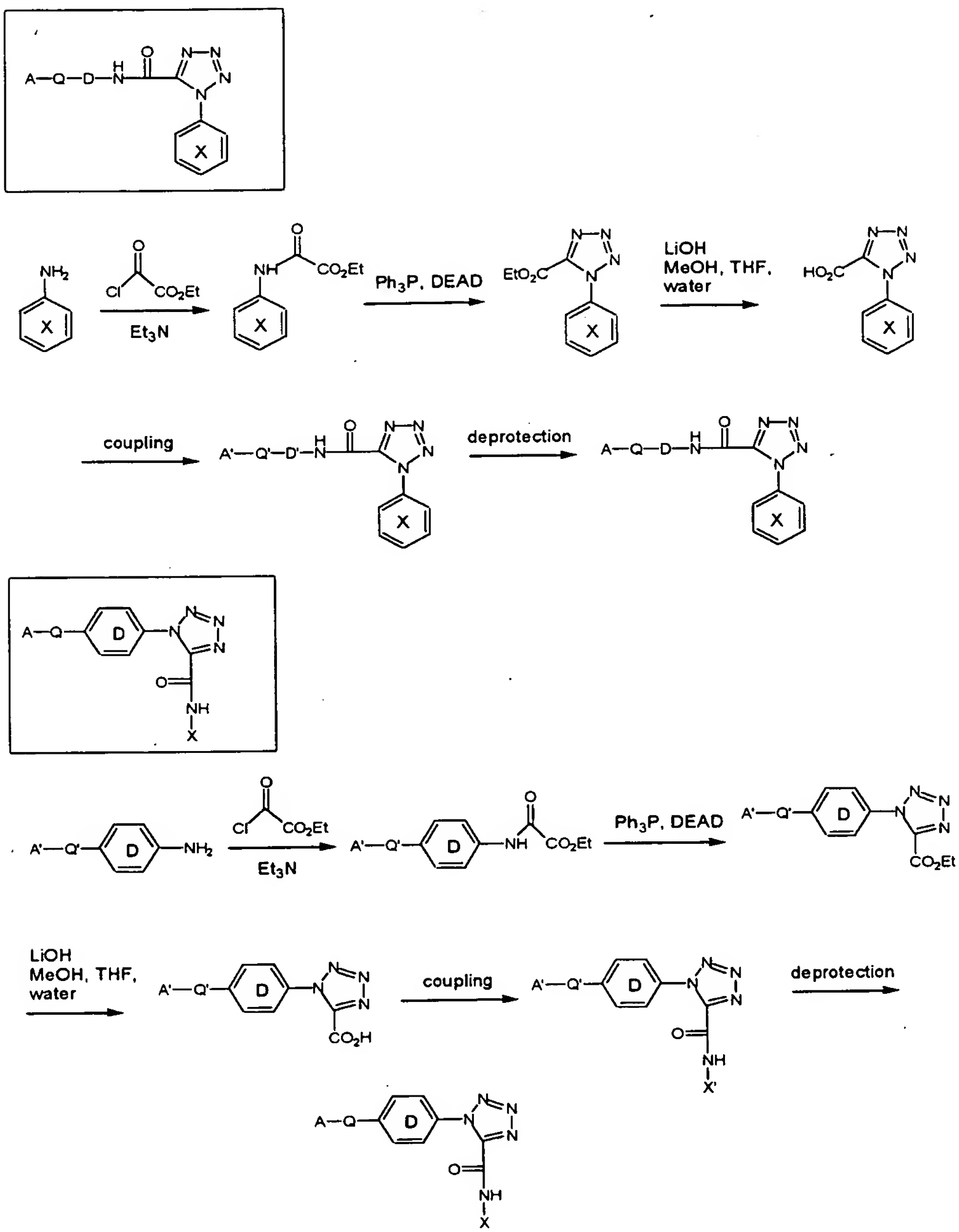




Scheme 4 shows the general synthesis of compounds with a N-linked tetrazole G ring. An appropriately protected aromatic amine is acylated with ethyl chlorooxoacetate. The resulting amide can be converted to the tetrazole by a literature method (Journal of Organic Chemistry, 56, 2395 (1991)). Other methods (Synthesis, 767 (1993); Journal of Organic Chemistry, 58, 32 (1993); Bioorganic & Medicinal Chemistry Letters, 6, 1015 (1996)) can also be used.

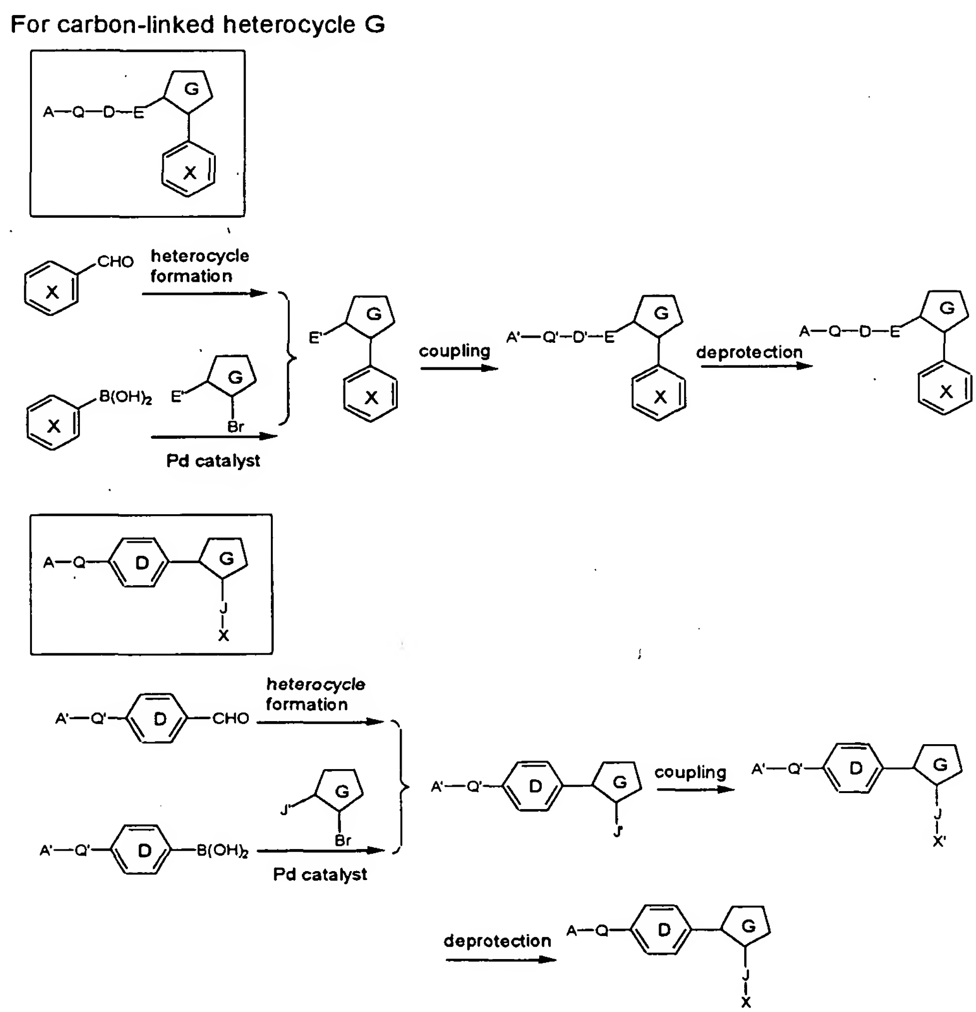
Scheme 4

For tetrazole-linked compounds



General synthesis for compounds with a C-linked G ring is outlined in Scheme 5. A', Q', D', E', J' and X' are protected functional structures which can be converted to A, Q, D, E, J and X respectively. For formation of the C-linked G ring, the appropriate aromatic aldehyde precursor is treated under conditions described in Joule, Mills and Smith, "Heterocyclic Chemistry", Chapman & Hall, London, 1995, or the references cited therein, or as described later in the preparation section to give the G ring. The C-linked G ring can also be connected to aromatic X or aromatic D using Suzuki cross-coupling method (Chemical Reviews, 95, 2457 (1995)).

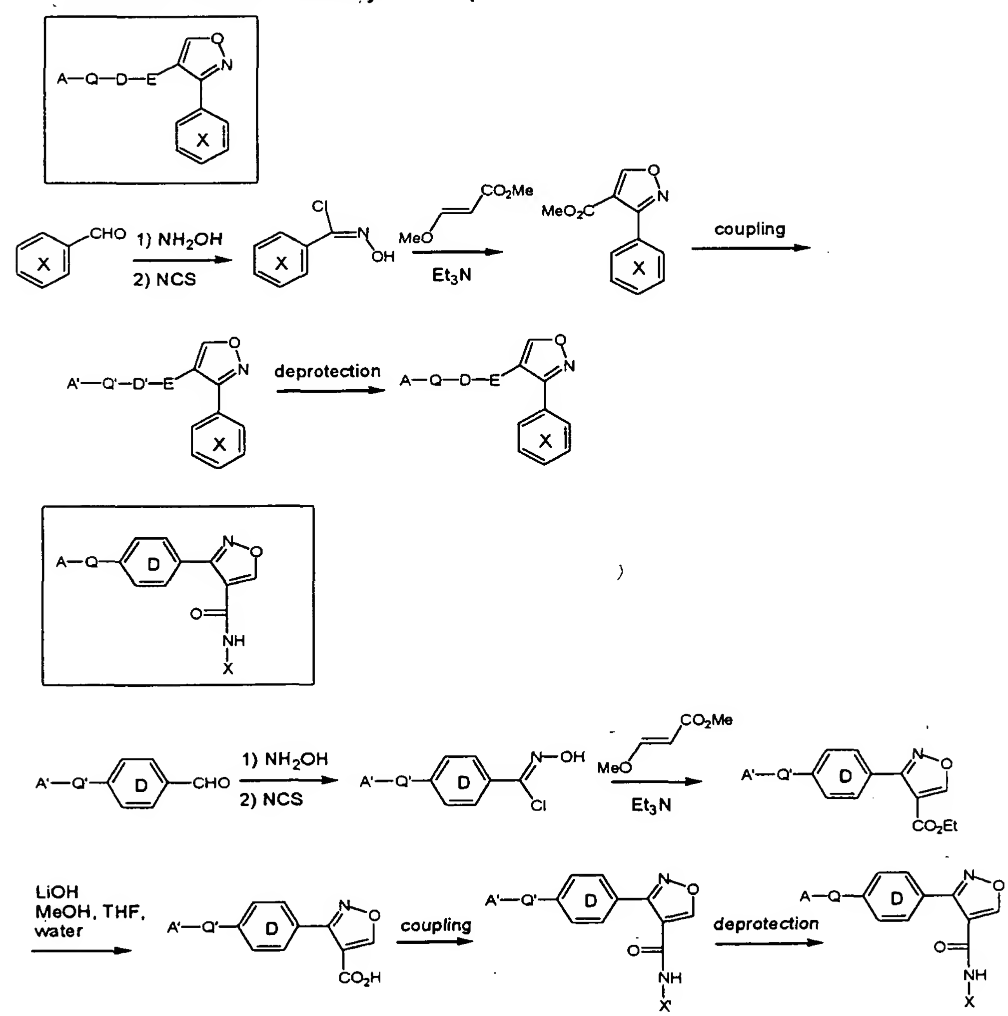
Scheme 5



Scheme 6 shows the general synthesis of compounds with a C-linked isoxazole G ring. A substituted aromatic aldehyde is reacted with hydroxylamine and then chlorinated to yield the hydroximinoyl choride (Journal of Organic Chemistry, 45, 3916 (1980)). It is treated with triethylamine to generate nitrile oxide in situ, which is reacted with methyl *trans*-3-mthoxyacrylate or methyl propiolate to give the isoxazole structure (Chemical Letters, 1, 85 (1987)).

Scheme 6

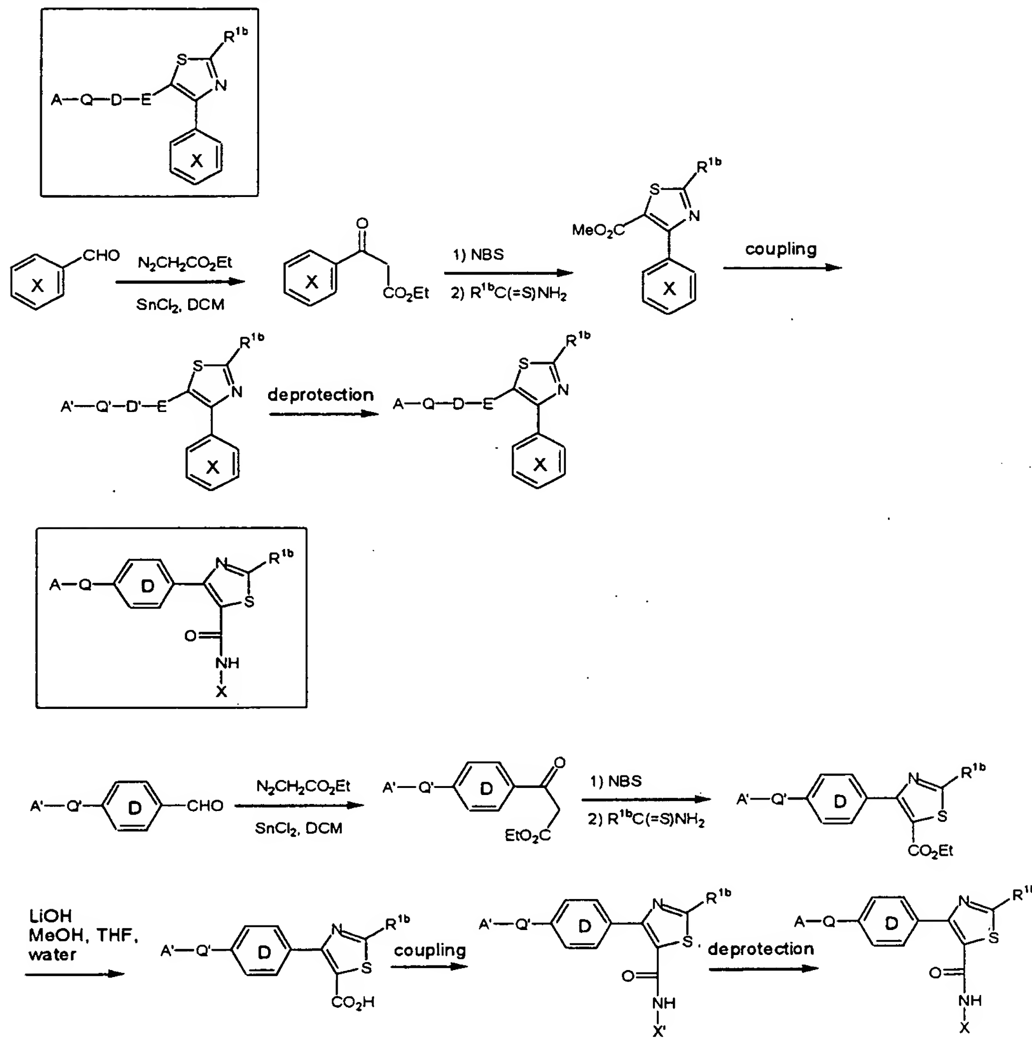
For isoxazole-linked hetereocycle compounds



Scheme 7 shows the general synthesis of compounds with a C-linked thiozole G ring. A substituted aromatic aldehyde is reacted with ethyl diazoacetate in presence of tin(II) chloride to afford the beta-ketoester. It is then converted to thiazole.

Scheme 7

For thiazole-linked hetereocycle compounds



Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinalpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between about 3 and about 11, more preferably from about 5 to about 9 and most preferably from about 7 to about 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical

formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual

determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to about 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above

materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also

characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not); thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications

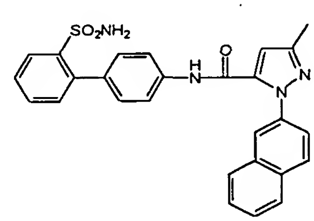
associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

Examples

Example 1.



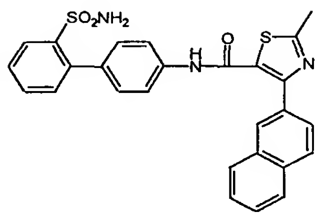
Step 1. To the solution of 2-naphthylboronic acid (5.00 g, 29.1 mmol) and ethyl 3-methylpyrazole-5-carboxylate (4.48 g, 29.1 mmol) in 100 mL dry dichloromethane

(DCM) were added pyridine (4.7 mL, 58.2 mmol) and anhydrous powder of copper(II) acetate (7.94 g, 43.7 mmol). Some activated molecular sieve powder was added afterwards. The resulting slurry was stirred for 2 days under argon. The mixture was diluted with DCM. It was filtered through a celite bed. The blue filtrate was washed with water (X2), dried over $MgSO_4$, concentrated, purified by silica column to yield ethyl 3-methyl-1-(2-naphthyl)-1H-pyrazole-5-carboxylate and its regioisomer in a 1:1 ratio in 70% yield. Rf 0.59 (1:2 EtOAc: hexane), M+H 281; regioisomer, ethyl 5-methyl-1-(2-naphthyl)-1H-pyrazole-3-carboxylate, Rf 0.44 (1:2 EtOAc: hexane). ES-MS: $(M+H)^+$ 281.

Step 2. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (50 mg, 0.16 mmol) in 1 mL DCM was added trimethylaluminum (2.0M in hexane, 0.41 mL, 0.82 mmol) under argon at room temperature. After being stirred for 30 minutes, to the mixture was added the above-prepared ester (46 mg, 0.16 mmol) in 1 mL DCM. The resulting mixture was stirred overnight. The reaction was quenched using 5 mL saturated Rochelle salt aq solution. The mixture was extracted using DCM (X3). The organic phases were combined, dried, rotovaped and subjected on flash column to give the coupled product in 52% yield (46 mg). Rf 0.46 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 539.

Step 3. The above-prepared compound (42 mg, 0.078 mmol) was placed in 3 mL trifluoroacetic acid (TFA). The solution was stirred in 60°C bath for 30 minutes. TFA was removed on rotovap. The residue was dissolved in methanol and purified by preparative HPLC to afford the title compound in 95% yield. ES-MS: $(M+H)^+$ 483.

Example 2.



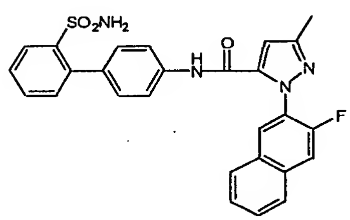
Step1. A mixture of tin(II) chloride (2.08 g, 10.96 mmol) and ethyl diazoacetate (2.76 mL, 26.28 mmol) in 50 mL DCM was stirred for 2 hours. Naphthalene-2-carbaldehyde was added. After stirred at room temperature for 18 hours, the mixture was concentrated, dissolved in EtOAc, washed with water (X3), dried and evaporated. The crude material was purified to give product ethyl 3-(2-naphthyl)-3-oxoprppionate. Rf 0.61 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 243.

Step 2. To a solution of the above-prepared ester (240 mg, 1 mmol) in 15 mL MeCN at 65°C was added hydroxy(tosyloxy)iodobenzene (430 mg, 1.1 mmol). After stirred for 1 hour, to the mixture was added thiourea (83 mg, 1.1 mmol). The resulting mixture was stirred overnight at 65°C. The solution was cooled and concentrated. The residue was dissolved in EtOAc, washed with brine, dried over $MgSO_4$, and evaporated to give crude 2-methyl-4-(2-naphthyl)-5-(carboethoxy)thiazole. Rf 0.64 (1:3 EtOAc: hexane). ES-MS: $(M+H)^+$ 298.

Step 3. To a solution of the above-prepared product (148 mg, 0.50 mmol) and 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (152 mg, 0.50 mmol) in 3 mL DCM was added trimethylaluminum (2.0M in hexane, 0.75 mL, 1.5 mmol), and the mixture was stirred at room temperature for 20 hours. The reaction was neutralized with 4 mL 1N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the coupling product (170 mg, 61%). Rf 0.25 (1:3 EtOAc: hexane). ES-MS: $(M+H)^+$ 556.

Step 4. The above-prepared product (100 mg) was placed in 3 mL TFA. The solution was stirred in 80°C bath for 60 minutes. TFA was removed on rotovap. The residue was dissolved in methanol and purified by preparative HPLC to afford the title compound in over 90% yield. ES-MS: $(M+H)^+$ 500.

Example 3.



Step 1. 3-Amino-2-naphthoic acid (40.4 g, 216 mmol) was placed in 200 mL concentrated HCl. At 0°C, the slurry was stirred vigorously using a mechanical stirring blade. To it was added a cold solution of sodium nitrite (29.8 g, 432 mmol) in 70 mL water. After completion, the cold slurry was stirred for 30 minutes at 0°C. To it was added cold tetrafluoroboric acid (48 wt. % in water, 56 mL, 432 mmol). After stirred at 0°C for 30 minutes, the solid was filtered using a Buchner funnel. The soild cake was carefully rinsed with cold water (10 mL X2), cold tetrafluoroboric acid (10 mL X2) and cold ethanol (5 mL X2). The solid was dried in vacuuo. It was then placed in 300 mL xylene and refluxed overnight. Xylene was removed on rotovap. The residue was acidified to pH1 with aq HCl and taken into EtOAc. It was washed with brine (X2), dried, evaporated to give 3-fluoro-2-naphthoic acid (32.6 g, 78%). ES-MS: $(M+H)^+$ 191.

Step 2. The above-prepared acid (14.7 g, 77 mmol) was dissolved in 200 mL $CHCl_3$. To it was added 0.5 mL dry DMF. Then at room temperature, oxalyl chloride (20 mL, 232 mmol) was added dropwise. The reaction solution was stirred for overnight. All solvent was removed in vacuuo. The residue was pumped till dryness. It was

dissolved in 150 mL dry dioxane, chilled to 0°C and vigorously stirred. To it, at the cold tempareture, was added the cold solution of sodium azide (10 g, 155 mmol, in 30 mL water and 15 mL dioxane) in small portions. The reaction was allowed for 2 hours at 0°C. The solvent was removed in vacuuo. The residue was taken into EtOAc and washed with brine (X3). The organic phase was dried and evaporated to dryness in vacuuo to give 3-fluoro-2-naphthoyl azide. Rf 0.83 (1:1 EtOAc: hexane). It was dissolved in 80 mL DMF. To it was added 40 mL water. The milky mixture was refluxed overnight. The solvent was removed in vacuuo. The residue was taken into EtOAc, and washed with brine (X2). The organic phase was dried, concentrated and purified with flash silica column to yield 3-fluoro-2-naphthylamine (8.1 g, 65%). Rf 0.40 (1:3 EtOAc: hexane). ES-MS: $(M+H)^+$ 162.

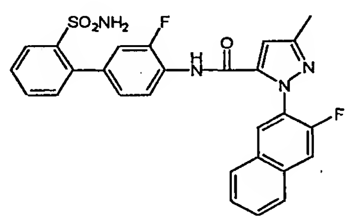
Step 3. The above-prepared compound (7.5 g, 46 mmol) was placed in 50 mL concentrate HCl. The mixture was vigorously stirred in ice bath. To it was dropwise added cold sodium nitrite (3.8 g, 55 mmol) solution in 10 mL water. After completion, the mixture was stirred at 0°C for half an hour. At 0°C, to it was dropwise added cold $SnCl_2.2H_2O$ (26.3 g, 116 mmol) solution in 20 mL concentrate HCl. The slurry was stirred for half an hour at 0°C, chilled, and filtered through a Buchner funnel to isolate the solid hydrazine. It was dried in vacuuo. The solid hydrazine was dissolved in 100 mL glacial acetic acid. To it were added ethyl 2-N-(methoxy)imino-4-oxopentanoate (10.4 g, 56 mmol, prepared from ethyl 2,4-dioxovalerate and methoxylamine hydrogen chloride in ethanol) and 50 mL THF. The mixture was refluxed for 2 hours. The solvent was removed in vacuuo. The residue was taken into EtOAc, washed with brine and water. The organic phase was dried, concentrated and purified with flash column to yield ethyl 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylate (9.0 g, 65%). Rf 0.52 (1:2 EtOAc: hexane). ES-MS: $(M+H)^+$ 299.

Step 4. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (77mg, 0.25 mmol) in 1 mL dry DCM was added trimethylaluminum (2.0M in

hexane, 0.51 mL, 1.0 mmol). The mixture was stirred for 20 minutes. The above-prepared ester (50 mg, 0.17 mmol) was dissolved in 3 mL dry DCM and added into the aluminum mixture. The reaction was stirred at room temperature for overnight and quenched using saturated Rochelle's salt aq solution. It was extracted with $CHCl_3$ (X3). The organic phases were combined, dried, concentrated and purified with flash column to yield the coupling product (85 mg, 90%). Rf 0.45 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 557.

Step 5. The above-prepared product was placed into 3 mL TFA. The mixture was stirred overnight at room temperature. It was evaporated, dissolved in methanol, purified with prep HPLC to afford the title compound in over 90% yield.). ES-MS: $(M+H)^+$ 501.

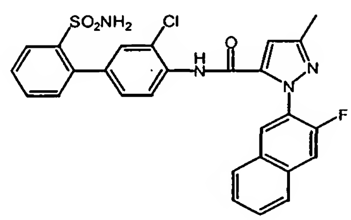
Example 4.



Step 1. The preparation of ethyl 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylate was the same as that in Step 3 for Example 3. This ester (13.2 g, 44 mmol) was dissolved in 80 mL methanol. To it were added $LiOH.H_2O$ (3.7 g, 49 mmol) and 40 mL water. The mixture was stirred for overnight at room temperature. It was evaporated in vacuuo to remove methanol. The residue was acidified with 1N HCl till pH 1. The mixture was extracted with EtOAc (X4). The organic extracts were combined, dried, evaporated and pumped to dryness to afford 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazolecarboxylic acid in over 90% yield. ES-MS: $(M+H)^+$ 271.

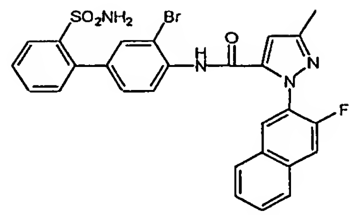
Step 2. The above-prepared acid (33 mg, 0.12 mmol), 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine (77 mg, 0.24 mmol) and catalytic amount of DMAP (5 mg) were dissolved in 2 mL pyridine. The solution was stirred at 0°C. To it was added $POCl_3$ (45μL, 0.48 mmol). The mixture was stirred for 1 hour and quenched with ice chips. To it was added EtOAc. It was washed with brine (X2), dried, and concentrated. To the residue was added 3 mL TFA. The mixture was stirred at 60°C for 1 hour, concentrated, dissolved in methanol and subjected on prep HPLC to afford the title compound in 50% yield (31 mg). ES-MS: $(M+H)^+$ 519.

Example 5.



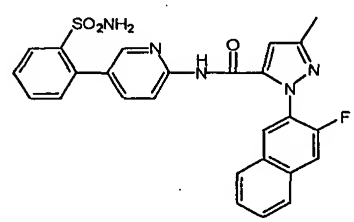
This compound was prepared by the same methodology described for Example 4 with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 535.

Example 6.



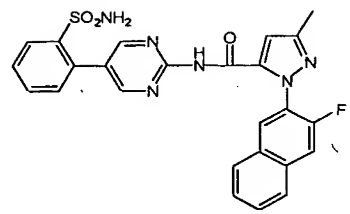
This compound was prepared by the same methodology described for Example 4 with 2'-N-tert-butylaminosulfonyl-3-bromo-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 579, 581 (Br pattern).

Example 7.



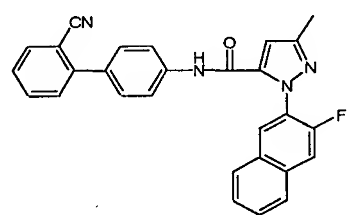
This compound was prepared by the same methodology described for Example 4 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 502.

Example 8.



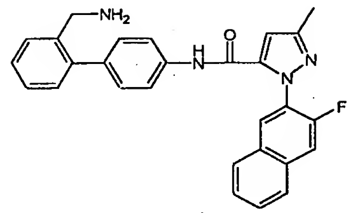
This compound was prepared by the same methodology described for Example 4 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyrimidine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 503.

Example 9.



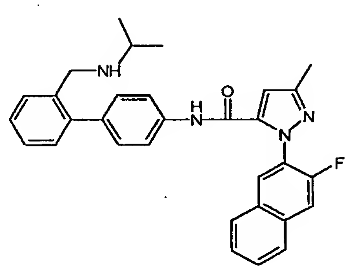
This compound was prepared by the same methodology described for Example 4 with 2'-cyano-[1,1']-biphenyl-4-ylamine substituted 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the TFA treatment. ES-MS: $(M+H)^+$ 447.

Example 10.



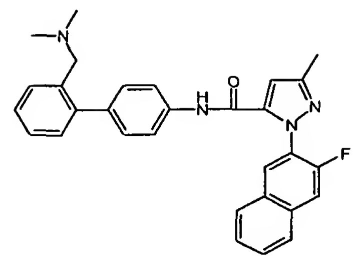
The title compound (40 mg, 0.09 mmol) of Example 9 was dissolved in 2 mL dry DMF. At 0°C, to it were added sodium borohydride (27 mg, 0.72 mmol) and anhydrous Co(II) chloride (23 mg, 0.18 mmol). The mixture was stirred for 2 hours and quenched with 1 mL acetic acid. The mixture was evaporated, dissolved in methanol, filtered, loaded on prep HPLC to afford the title compound in 60% yield. ES-MS: $(M+H)^+$ 451.

Example 11.



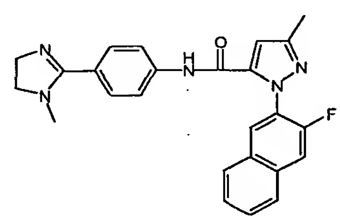
The title compound (40 mg, 0.09 mmol) of Example 9 was dissolved in 2 mL dry DMF. At 0°C, to it were added sodium borohydride (27 mg, 0.72 mmol) and anhydrous Co(II) chloride (23 mg, 0.18 mmol). The mixture was stirred for 2 hours. To it was added 10 mL acetone. The mixture was stirred for 1 hour at room temperature. The reaction was quenched with 1 mL acetic acid. The mixture was evaporated, dissolved in methanol, filtered, loaded on prep HPLC to afford the title compound in 50% yield. ES-MS: $(M+H)^+$ 493.

Example 12.



This compound was prepared by the same methodology described for Example 4 with 2'-(N-dimethylamino)methyl-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the TFA treatment. ES-MS: $(M+H)^+$ 479.

Example 13.

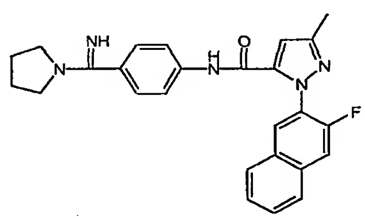


Step 1. The preparation of 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazolecarboxylic acid was the same as that in Step 1 of Example 4.

Step2. This acid (65 mg, 0.24 mmol), 4-aminobenzonitrile (57 mg, 0.48 mmol) and DMAP (5 mg) were dissolved in 3 mL pyridine. The solution was stirred at 0°C. To it was added $POCl_3$ (90 µL, 0.96 mmol). The mixture was stirred for 1 hour. The reaction was then quenched with ice chips. It was diluted with EtOAc. The organic phase was washed with brine (X2). It was dried, concentrated and purified with flash column to afford the coupling product (60 mg, 68%). Rf 0.40 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 371.

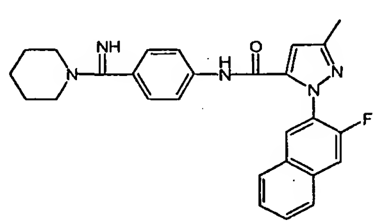
Step 3. The above-prepared nitrile was dissolved in 10 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached (indicated by a blown-up balloon attached on the top of the reaction flask). The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 403. The solvent was removed in vacuuo. The residue was pumped to dryness. The solid was dissolved in 5 mL dry methanol. To it was added anhydrous N-methylethylenediamine (0.5 mL). The mixture was refluxed for 1 hour, concentrated and loaded on prep HPLC to afford the title compound in 80% yield. ES-MS: $(M+H)^+$ 428.

Example 14.



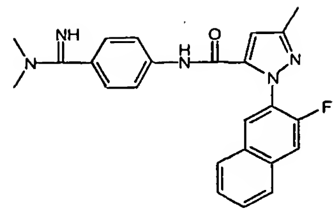
This compound was prepared by the same methodology described for Example 13 with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 442.

Example 15.



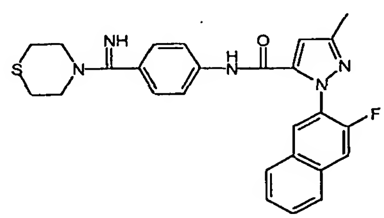
This compound was prepared by the same methodology described for Example 13 with piperidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 456.

Example 16.



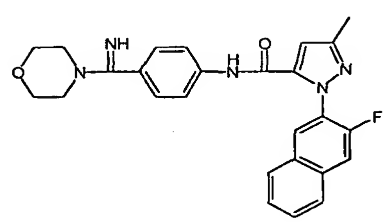
This compound was prepared by the same methodology described for Example 13 with dimethylamine (commercial 2M solution in THF) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 416.

Example 17.



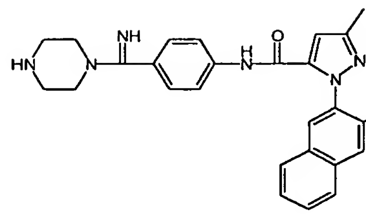
This compound was prepared by the same methodology described for Example 13 with thiomorpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 474.

Example 18.



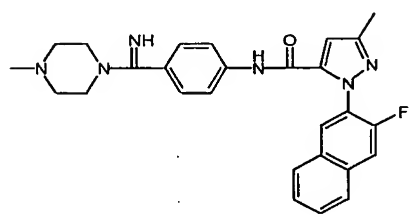
This compound was prepared by the same methodology described for Example 13 with morpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 458.

Example 19.



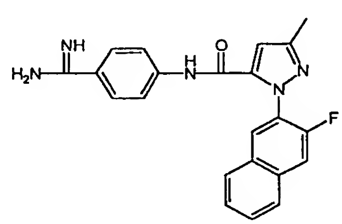
This compound was prepared by the same methodology described for Example 13 with piperazine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 457.

Example 20.



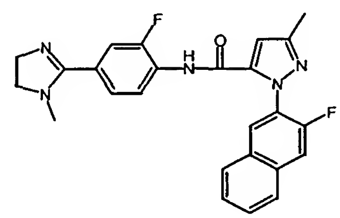
This compound was prepared by the same methodology described for Example 13 with N-methylpiperazine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 471.

Example 21.



This compound was prepared by the same methodology described for Example 13 with ammonium acetate substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 388.

Example 22.



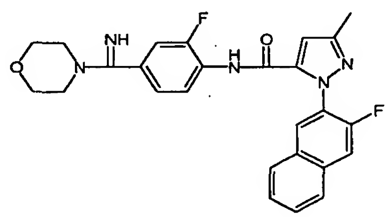
Step 1. 2-Fluoro-4-iodoaniline (5.0 g, 21 mmol) was dissolved in 20 mL dry DMF. To it were added CuCN (3.8 g, 42 mmol) and catalytic amount of CuI (200 mg). The slurry was refluxed for 1 hour. Diluted with EtOAc. Filtered through celite. Concentrated in vacuuo to yield solid 4-amino-3-fluorobenzonitrile (2.9 g, 100%). ES-MS: $(M+H)^+$ 137.

Step 2. The preparation of 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazolecarboxylic acid was the same as that in Step 1 of Example 4. This acid (270 mg, 1.0 mmol), 4-amino-3-fluorobenzonitrile (272 mg, 2.0 mmol) and DMAP (10 mg) were dissolved in 15 mL pyridine. The solution was stirred at 0°C. To it was added $POCl_3$ (380 µL, 4.0 mmol). The mixture was stirred for 1 hour. The reaction was then quenched with ice chips. It was diluted with EtOAc. The organic phase was washed with brine (X2). It was dried, concentrated and purified with flash column to afford the coupling product (350 mg, 97%). Rf 0.77 (7:3 EtOAc: hexane). ES-MS: $(M+H)^+$ 389.

Step 3. The above-prepared nitrile (30 mg, 0.077 mmol) was dissolved in 10 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached (indicated by a blown-up balloon attached on the top of the reaction flask). The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 421. The solvent was removed in vacuuo. The residue was pumped

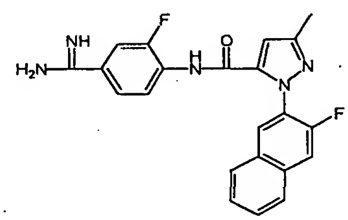
This compound was prepared by the same methodology described for Example 22 with hexamethyleneimine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 488.

Example 26.



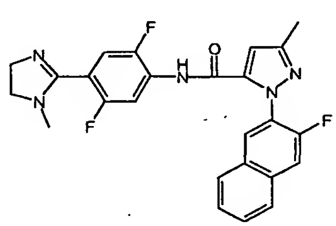
This compound was prepared by the same methodology described for Example 22 with morpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 476.

Example 27.



This compound was prepared by the same methodology described for Example 22 with ammonium acetate substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 406.

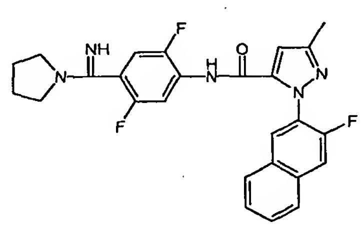
Example 28.



Step 1. The preparation of 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazolecarboxylic acid was the same as that in Step 1 of Example 4. This acid (50 mg, 0.18 mmol), 4-amino-2,5-difluorobenzonitrile (57 mg, 0.36 mmol) and DMAP (5 mg) were dissolved in 8 mL pyridine. The solution was stirred at 0°C. To it was added $POCl_3$ (70 µL, 0.74 mmol). The mixture was stirred for 1 hour. The reaction was then quenched with ice chips. It was diluted with EtOAc. The organic phase was washed with brine (X2). It was dried, concentrated and purified with flash column to afford the coupling product (70 mg, 93%). Rf 0.69 (7:3 EtOAc: hexane). ES-MS: $(M+H)^+$ 407.

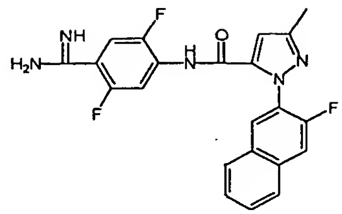
Step 2. The above-prepared nitrile (30 mg, 0.074 mmol) was dissolved in 10 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached (indicated by a blown-up balloon attached on the top of the reaction flask). The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 439. The solvent was removed in vacuuo. The residue was pumped to dryness. The solid was dissolved in 5 mL dry methanol. To it was added anhydrous N-methylethylenediamine (0.5 mL). The mixture was refluxed for 1 hour, concentrated and loaded on prep HPLC to afford the title compound in 80% yield. ES-MS: $(M+H)^+$ 464.

Example 29



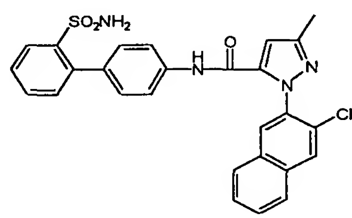
This compound was prepared by the same methodology described for Example 28 with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 478.

Example 30.



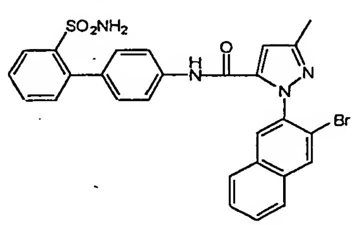
This compound was prepared by the same methodology described for Example 28 with ammonium acetate substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 424.

Example 31.



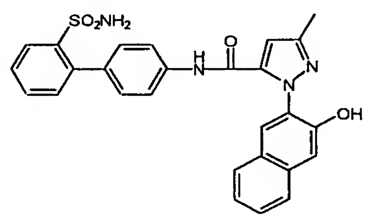
This compound was prepared by the same methodology from Step 3 to Step 5 described for Example 3 with 3-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 517.

Example 32.



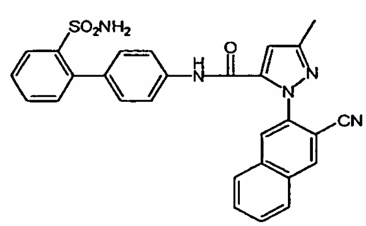
This compound was prepared by the same methodology from Step 3 to Step 5 described for Example 3 with 3-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 561, 563 (Br pattern).

Example 33.



This compound was prepared by the same methodology from Step 3 to Step 5 described for Example 3 with 3-hydroxy-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 499.

Example 34.



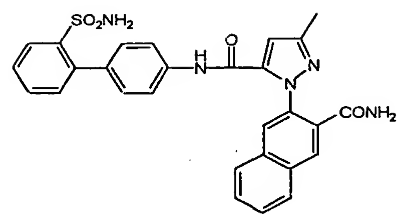
Step 1. The synthesis of ethyl 3-methyl-1-(3-bromo-2-naphthyl)-1H-pyrazole-carboxylate followed the same methodology described for Step 3 of Example 3 with commercial with 3-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. Yield 60%. Rf 0.42 (1:3 EtOAc: hexane). ES-MS: $(M+H)^+$ 359, 361 (Br pattern).

Step 2. The above-prepared bromide (370 mg, 1.0 mmol) was dissolved in 3 mL dry DMF. To it were added CuCN (180 mg, 2.0 mmol) and CuI (20 mg). The slurry mixture was refluxed for 2 hours. It was diluted with EtOAc. Filtered through celite. Concentrated and purified by flash column to yield of ethyl 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-carboxylate (220 mg, 70%). Rf 0.48 (1:2 EtOAc: hexane).). ES-MS: $(M+H)^+$ 306.

Step 3. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (164 mg, 0.54 mmol) in 2 mL dry DCM was added trimethylaluminum (2.0M in hexane, 1.1 mL, 2.2 mmol). The mixture was stirred for 20 minutes. The above-prepared ester (137 mg, 0.45 mmol) was dissolved in 6 mL dry DCM and added into the aluminum mixture. The reaction was stirred at room temperature for overnight and quenched using saturated Rochelle's salt aq solution. It was extracted with $CHCl_3$ (X3). The organic phases were combined, dried, concentrated and purified with flash column to yield 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide (170 mg, 67%). Rf 0.40 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 564.

Step 4. The above-prepared compound (30 mg, 0.05 mmol) was dissolved in 5 mL dry DCM. At 0°C, to it was added $BF_3.OEt_2$ (62 μL, 0.5 mmol) dropwise. The mixture was stirred overnight. Extra 1.0 mmol $BF_3.OEt_2$ was added in small portions at room temperature the next day. After another overnight, deprotection was about 70% complete. The mixture was loaded on a short flash column for separation. The title product was purified using prep HPLC (55% yield). ES-MS: $(M+H)^+$ 508.

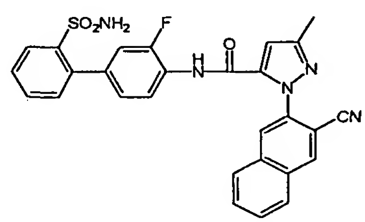
Example 35.



Step 1. The synthesis of 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide followed the same procedure of Step 3 for Example 34.

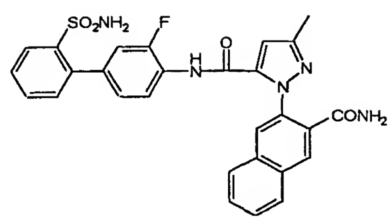
Step 2. The above-prepared compound (30 mg, 0.05 mmol) was placed in 3 mL TFA and refluxed for 1 hour. After concentration, it was purified with prep HPLC to yield the title compound (85%). ES-MS: $(M+H)^+$ 526.

Example 36



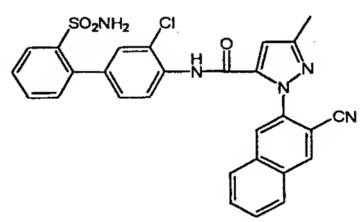
This compound was prepared by the same methodology described for Example 34 with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 526.

Example 37.



This compound was prepared by the same methodology described for Example 35 with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 544.

Example 38



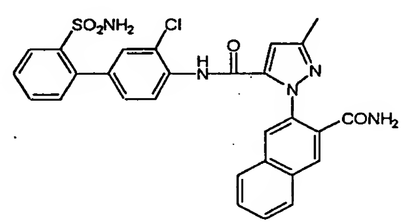
Step 1. The synthesis of ethyl 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-carboxylate followed the same procedure of Step 2 for Example 34.

Step 2. The above-prepared ester (930 mg, 3.0 mmol) was dissolved in 20 mL methanol. To it were added $LiOH.H_2O$ (256 mg, 6.0 mmol) and 10 mL water. The mixture was stirred for 3 hours at room temperature. Methanol was removed in vacuuo. The residue was carefully acidified with 1N HCl till pH 1. It was extracted with EtOAc (X4). The organic phases were combined, dried and evaporated in vacuuo till dryness to give 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-carboxylic acid (720 mg, 85%). ES-MS: $(M+H)^+$ 278.

Step 3. The mixture of the above-prepared acid (110 mg, 0.40 mmol), 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine (0.21 g, 0.60 mmol), DMAP (5 mg) were dissolved in 5 mL pyridine and stirred at 0°C. To it was added $POCl_3$ (120 μL, 1.2 mmol). The mixture was stirred for 2.5 hours and quenched with ice chips. It was diluted with EtOAc, washed with brine (X2), dried, concentrated and purified with flash column to give 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphen-4-yl))carboxyamide (240 mg, 95%). Rf 0.65 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 598.

Step 4. The above-prepared compound (30 mg, 0.05 mmol) was dissolved in 5 mL dry DCM. At 0°C, to it was added $BF_3.OEt_2$ (62 μL, 0.5 mmol) dropwise. The mixture was stirred overnight. Extra 1.0 mmol $BF_3.OEt_2$ was added in small portions at room temperature the next day. After another overnight, deprotection was about 70% complete. The mixture was loaded on a short flash column for separation. The title product was purified using prep HPLC (52% yield). ES-MS: $(M+H)^+$ 542.

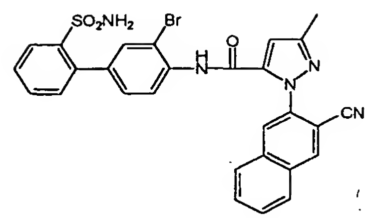
Example 39.



Step 1. The synthesis of 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphen-4-yl))carboxyamide followed the same procedure of Step 3 for Example 38.

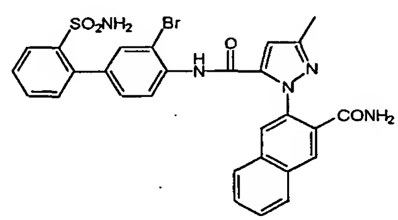
Step 2. The above-prepared compound (30 mg, 0.05 mmol) was placed in 3 mL TFA and refluxed for 1 hour. After concentration, it was purified with prep HPLC to yield the title compound (85%). ES-MS: $(M+H)^+$ 560.

Example 40



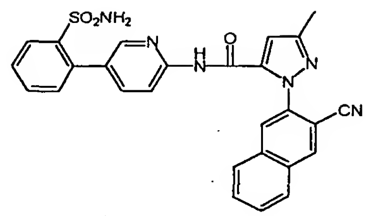
This compound was prepared by the same methodology described for Example 38 with 2'-N-tert-butylaminosulfonyl-3-bromo-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 586, 588 (Br pattern).

Example 41.



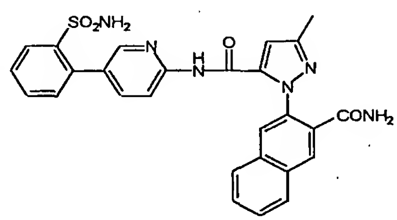
This compound was prepared by the same methodology described for Example 39 with 2'-N-tert-butylaminosulfonyl-3-bromo-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 604, 606 (Br pattern).

Example 42



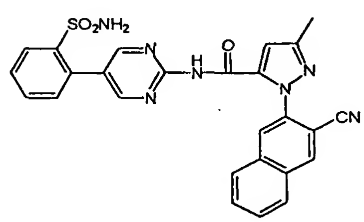
This compound was prepared by the same methodology described for Example 38 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 509.

Example 43.



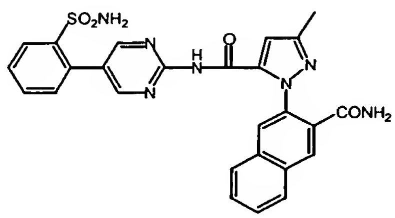
This compound was prepared by the same methodology described for Example 39 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 527.

Example 44



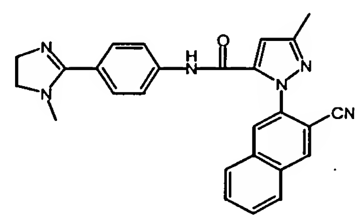
This compound was prepared by the same methodology described for Example 38 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyrimidine substituted for 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 510.

Example 45.



This compound was prepared by the same methodology described for Example 39 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyrimidine substituted for 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 528.

Example 46.

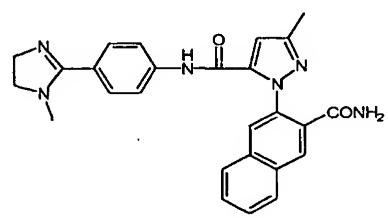


Step 1. To a solution of 4-nitroaniline (1.0 g, 6.7 mmol) in 50 mL anhydrous ethanol at 0°C was bubbled dry HCl gas via a long needle till saturation reached. The resulting solution was stirred overnight. The solvent was removed in vacuuo. The residue was pumped to dryness. It was dissolved in 50 mL anhydrous ethanol. To it was added 2 mL N-methylethylenediamine. The mixture was refluxed for 1 hour and evaporated in vacuuo to give the 1-methyl-2-(4-nitrophenyl)-2-imidazoline HCl salt in 90% yield. ES-MS: $(M+H)^+$ 206.

Step 2. To a solution of the above-prepared nitro compound (500 mg, 2.4 mmol) in 4 mL 4N HCl and 50 mL methanol was added 10% Pd/C (50 mg). The mixture was stirred for 2 hours under a hydrogen balloon. It was filtered through celite and concentrated in vacuuo to give the 4-(1-methyl-2-imidazolin-2-yl)aniline HCl salt in 90% yield. ES-MS: $(M+H)^+$ 176.

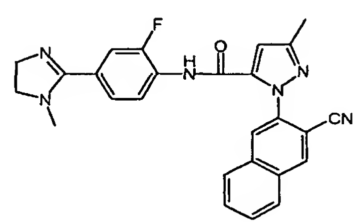
Step 3. To a solution of the above-prepared amine (40 mg, 0.22 mmol), 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-carboxylic acid (15 mg, 0.054 mmol, see Step 2, Example 38), DMAP (2 mg) in 2 mL pyridine at 0°C was added $POCl_3$ (20 µL, 0.22 mmol). The mixture was stirred for 2 hours. It was concentrated in vacuuo and loaded on prep HPLC to afford the title compound in 60% yield. ES-MS: $(M+H)^+$ 435.

<u>Example 47.</u>



The title compound in Example 46 (10 mg) was placed in TFA. It was refluxed for 1 hour and subjected on prep HPLC purification to afford the title compound in 85% yield. ES-MS: $(M+H)^+$ 453.

<u>Example 48.</u>

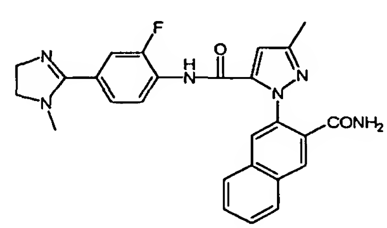


Step 1. To a solution of 2-fluoro-4-nitroaniline (300 mg, 2.2 mmol) in 20 mL anhydrous methanol at 0°C was bubbled dry HCl gas via a long needle till saturation reached. The resulting solution was stirred overnight. The solvent was removed in vacuuo. The residue was pumped to dryness. It was dissolved in 10 mL anhydrous methanol. To it was added 1 mL N-methylethylenediamine. The mixture was refluxed for 1 hour and evaporated in vacuuo to give the 1-methyl-2-(2-fluoro-4-nitrophenyl)-2-imidazoline HCl salt in 90% yield. ES-MS: $(M+H)^+$ 224.

Step 2. To a solution of the above-prepared nitro compound in 2 mL 4N HCl and 25 mL methanol was added 10% Pd/C (20 mg). The mixture was stirred for 2 hours under a hydrogen balloon. It was filtered through celite and concentrated in vacuuo to give the 2-fluoro-4-(1-methyl-2-imidazolin-2-yl)aniline HCl salt in 90% yield. ES-MS: $(M+H)^+$ 194.

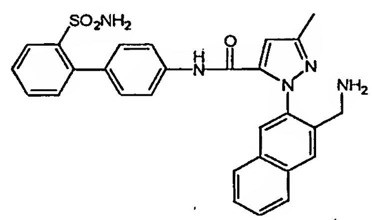
Step 3. To a solution of the above-prepared amine (100 mg, 0.51 mmol) in 2 mL DCM was added trimethylaluminum (2.0M in hexane, 2 mL, 4.0 mmol). The mixture was stirred for 20 minutes. Ethyl 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-carboxylate (76 mg, 0.25 mmol, see Step 2 of Example 34) was dissolved in 2 mL DCM and added into the reaction flask. The mixture was stirred for 2 days at room temperature. It was quenched with saturated Rochelle's salt aq solution and extracted with $CHCl_3$ (X4). The organic phases were combined, dried, concentrated and purifed with prep HPLC to yield the title compound (55%). ES-MS: $(M+H)^+$ 453.

<u>Example 49.</u>



The title compound in Example 48 (10 mg) was placed in TFA. It was refluxed for 1 hour and subjected on prep HPLC purification to afford the title compound in 85% yield. ES-MS: $(M+H)^+$ 471.

Example 50.

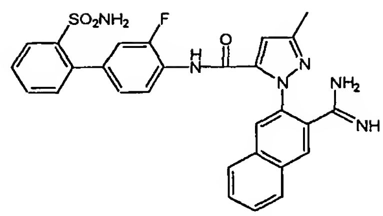


Step 1. Compound 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide was prepared by the same procedure shown in Step 3 of Example 34.

Step 2. The above-prepared compound (70 mg, 0.12 mmol) was dissolved in 2 mL dry DMF. At 0°C, to it were added sodium borohydride (36 mg, 0.96 mmol) and $CoCl_2$ (32 mg, 0.24 mmol). It was stirred for 2 days. Diluted with EtOAc and stirred for 1 hour. The mixture was filtered through celite. The filtrate was evaporated to give crude 3-methyl-1-(3-aminomethyl-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide. ES-MS: $(M+H)^+$ 568.

Step 3. The above-prepared crude compound was taken into 3 mL TFA. The mixture was stirred for 1 hour at 60°C. The mixture was evaporated and subjected on prep HPLC to isolate the title compound (35% yield). ES-MS: $(M+H)^+$ 512.

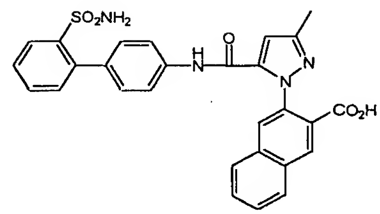
Example 51.



Step 1. Compound 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphen-4-yl))carboxyamide was prepared by the same methodology shown in Step 3 of Example 34, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 582.

Step 2. To a solution of the above-prepared compound (77 mg, 0.13 mmol) in 3 mL anhydrous methanol and 3 mL anhydrous EtOAc at -20°C was bubbled dry HCl gas via a long needle till saturation reached. The mixture was stirred for overnight. The solvent was removed in vacuuo. The dry residue was dissolved in 5 mL anhydrous methanol. To it was added 50 mg ammonium acetate. The mixture was refluxed for 2.5 hours. It was subjected on prep HPLC to isolate the title compound (55% yield). ES-MS: $(M+H)^+$ 543.

Example 52.



Step 1. 3-Amino-2-naphthoic acid (5.8 g, 31 mmol) was placed in 50 mL concentrate HCl. The slurry was vigorously stirred at 0°C. To it was added dropwise a cold solution of sodium nitrite (2.35 g, 34 mmol, in 14 mL water). After completion, the mixture was stirred for 40 minutes at 0°C. Under vigorously stirring, a cold solution of $SnCl_2.2H_2O$ (21 g, 93 mmol, in 30 mL concentrate HCl) was added dropwise. The mixture was stirred for 30 minutes and chilled in ice bath. The crude 3-carboxyl-2-naphthylhydrazine was collected with a Buchner funnel and pumped to dryness in vacuuo.

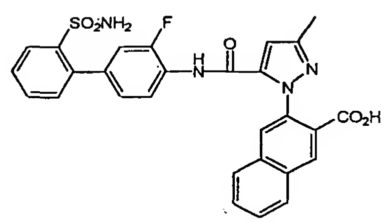
Step 2. The crude hydrazine prepared above was taken into 60 mL glacial acetic acid and 30 mL THF. To it was added ethyl 2-N-(methoxy)imino-4-oxopentanoate (2.6 g, 14 mmol). The mixture was refluxed for overnight. The solvent was removed in vacuuo. The residue was dissolved in EtOAc and washed with brine (X2). The organic phase was dried, concentrated and purified with flash column to yield ethyl 3-methyl-1-(3-carboxyl-2-naphthyl)-1H-pyrazole-5-carboxylate (4.1 g, 90%). Rf 0.15 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 325.

Step 3. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (36 mg, 0.12 mmol) in 1 mL dry DCM was added trimethylaluminum (2.0M in hexane, 0.5 mL, 1.0 mmol). The mixture was stirred for 20 minutes. The above-prepared ester (38 mg, 0.12 mmol) was dissolved in 3 mL dry DCM and added into the aluminum mixture. The reaction was stirred at room temperature for overnight and quenched using saturated Rochelle's salt aq solution. It was extracted with $CHCl_3$ (X3). The

organic phases were combined, dried, concentrated and purified with flash column to yield the coupling product (60%). ES-MS: $(M+H)^+$ 583.

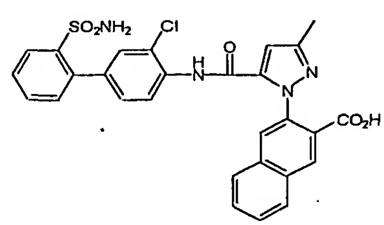
Step 4. The above-prepared compound (15 mg) was placed in 3 mL TFA and stirred overnight. It was concentrated and purified with prep HPLC to afford the title compound in 90% yield. ES-MS: $(M+H)^+$ 527.

Example 53.



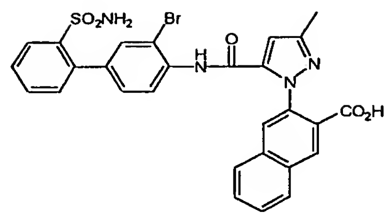
This compound was prepared by the same methodology described for Example 52 with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 545.

Example 54.



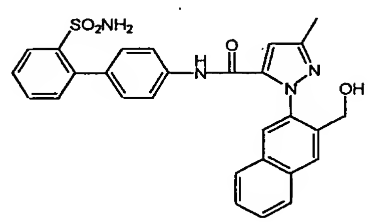
This compound was prepared by the same methodology described for Example 52 with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 561.

Example 55.



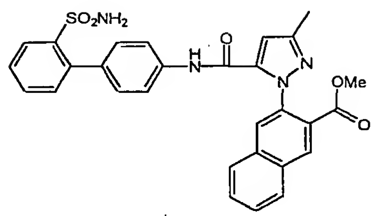
This compound was prepared by the same methodology described for Example 52 with 2'-N-tert-butylaminosulfonyl-3-bromo-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 605 and 607 (Br pattern).

Example 56.



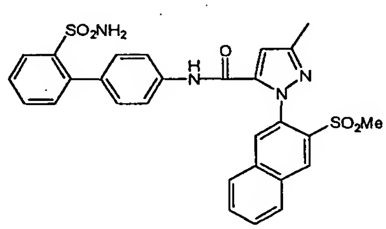
The title compound of Example 52 (14 mg, 0.027 mmol) was dissolved in 2 mL anhydrous THF. To it was added BH_3 (1M, 0.11 mL, 0.11 mmol) at 0°C. The mixture was stirred for 1 hour and quenched with acetic acid. The mixture was directly purified with prep HPLC to yield the title compound in 55% yield. ES-MS: $(M+H)^+$ 513.

Example 57.



The title compound of Example 52 (5 mg, 0.01 mmol) was dissolved in 1 mL anhydrous THF. To it was added $TMSCH_2N_2$ (2M, 0.01 mL, 0.02 mmol) at 0°C. The mixture was stirred for 1 hour at room temperature and quenched with TFA. The mixture was directly purified with prep HPLC to yield the title compound in 65% yield. ES-MS: $(M+H)^+$ 541.

Example 58.



Step 1. Compound ethyl 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylate was prepared using the procedure described in Step 3 of Example 3.

Step 2. The above-prepared fluoride (10.3 g, 34 mmol) was dissolved in 100 mL anhydrous DMSO. To it was added sodium thiomethoxide (27 g, 340 mmol). The mixture was stirred at 100°C for half an hour. The reaction was quenched with acetic acid. The mixture was evaporated to remove acetic acid, and was acidified using 5N HCl till pH 1 under vigorously stirring. It was extracted with EtOAc(X5). The organic phases were combined, dried and evaporated in vacuuo to afford crude 3-methyl-1-(3-

methylthio-2-naphthyl)-1H-pyrazole-5-carboxylic acid in over 90% yield. ES-MS: $(M+H)^+$ 299.

Step 3. The above-prepared crude acid was dissolved in 150 mL anhydrous ethanol. To it was added pTSA (3.3 g). The mixture was refluxed for 4 days till the esterification was over 95% complete. The solvent was removed in vacuuo. The residue was dissolved in EtOAc, washed with brine (X3), dried and purified by a short silica column to afford ethyl 3-methyl-1-(3-methylthio-2-naphthyl)-1H-pyrazole-5-carboxylate in over 80% yield. ES-MS: $(M+H)^+$ 327.

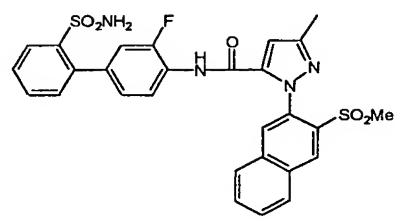
Step 4. The above-prepared ester (4.95 g, 15 mmol) was dissolved in 150 mL DCM. At 0°C, to the vigorously stirred solution was added MCPBA (11 g, 38 mmol) in small portions over 20 minutes. The reaction was allowed for 1 hour and diluted with $CHCl_3$. It was washed with $NaHCO_3$ saturated aq solution (X3), dried, concentrated and purified with flash column to give ethyl 3-methyl-1-(3-methylsulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylate (3.49 g, 65%). Rf 0.52 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 359.

Step 5. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (21 mg, 0.068 mmol) in 1 mL dry DCM was added trimethylaluminum (2.0M in hexane, 0.14 mL, 0.28 mmol). The mixture was stirred for 20 minutes. The above-prepared ester (16 mg, 0.045 mmol) in Step 4 was dissolved in 4 mL dry DCM and added into the aluminum mixture. The reaction was stirred at room temperature for overnight and quenched using saturated Rochelle's salt aq solution. It was extracted with $CHCl_3$ (X3). The organic phases were combined, dried, concentrated and purified with flash column to yield the coupling product (52%). Rf 0.17 (1:1 EtOAc: Hexane). ES-MS: $(M+H)^+$ 617.

Step 6. The above-prepared compound was dissolved in 2 mL acetonitrile and 2 mL TFA. The mixture was stirred for 1 hour at 70 C. The mixture was evaporated and

purified with prep HPLC to afford the title compound in 90% yield. ES-MS: $(M+H)^+$ 561.

Example 59.



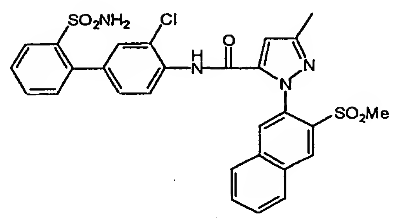
Step 1. The synthesis of ethyl 3-methyl-1-(3-methylsulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylate was the same as that described in Step 4 of Example 58.

Step 2. The above-prepared ester (3.4 g, 9.7 mmol) was dissolved in 20 mL methanol. To it were added $LiOH.H_2O$ (0.82 g, 19.5 mmol) and 10 mL water. The mixture was stirred at room temperature for overnight. The solvent was evaporated. The residue was acidified with 1N HCl till pH 1. The mixture was extracted with EtOAc (X4). The organic phases were combined, dried, evaporated to dryness to afford 3-methyl-1-(3-methylsulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid (3.24 g, 99%). ES-MS: $(M+H)^+$ 331.

Step 3. The above-prepared acid (102 mg, 0.31 mmol), 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine (150 mg, 0.46 mmol), DMAP (10 mg) were dissolved in 3 mL pyridine. To this stirred solution at 0°C was added $POCl_3$ (87 μL, 0.93 mmol). The mixture was stirred for 2 hours and quenched with ice chips. It was diluted with EtOAc, washed with brine (X2), dried, concentrated and purified with flash column to give the coupling product (130 mg, 66%). Rf 0.29 (1:1 EtOAc: hexane). MS: $(M+H)^+$ 635.

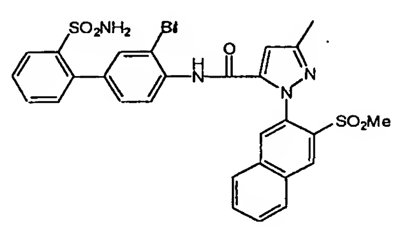
Step 4. The above-prepared compound (100 mg) was taken into 5 mL TFA and stirred at room temperature for overnight. After evaporation, the mixture was subjected on prep HPLC to isolate the title compound (90%). MS: $(M+H)^+$ 579.

Example 60.



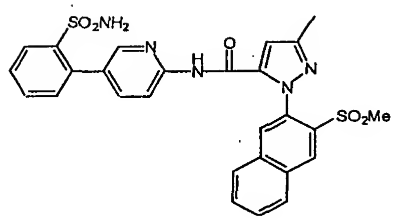
This compound was prepared by the same methodology described for Example 59 with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 595.

Example 61.



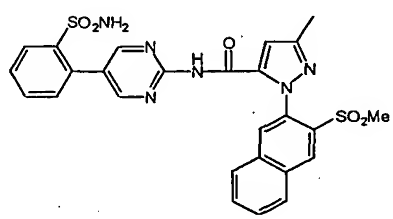
This compound was prepared by the same methodology described for Example 59 with 2'-N-tert-butylaminosulfonyl-3-bromo-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 639, 641 (Br pattern).

Example 62.



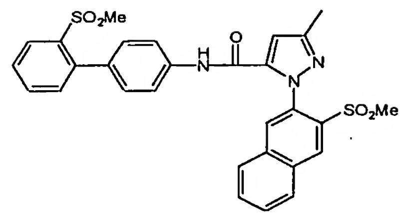
This compound was prepared by the same methodology described for Example 59 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 562.

Example 63.



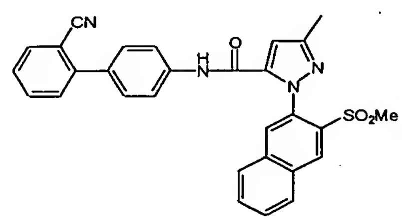
This compound was prepared by the same methodology described for Example 59 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyrimidine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 563.

Example 64.



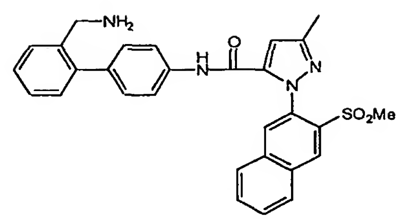
This compound was prepared by the same methodology described for Example 59 with for 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 560.

Example 65.



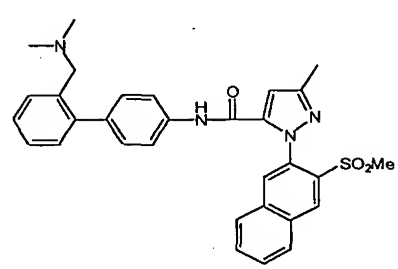
This compound was prepared by the same methodology described for Example 59 with for 2'-cyano-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 507.

Example 66.



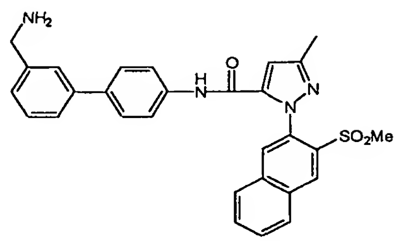
The title compound of Example 65 (55 mg, 0.11 mmol) was dissolved in 2 mL anhydrous DMF. To this stirred solution at 0°C were added sodium borohydride (33 mg, 0.88 mmol) and $CoCl_2$ (30 mg, 0.22 mmol). The reaction was allowed for 2 hours and quenched with acetic acid. The mixture was evaporated, diluted with EtOAc, and washed with $NaHCO_3$ aq solution. The organic phase was dried, evaporated and purified with prep HPLC to afford the title compound in 55% yield. ES-MS: $(M+H)^+$ 511.

Example 67.



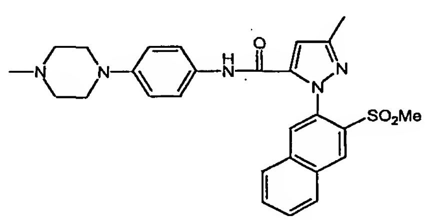
This compound was prepared by the same methodology described for Example 59 with for 2'-(N-dimethylaminomethyl)-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 539.

Example 68.



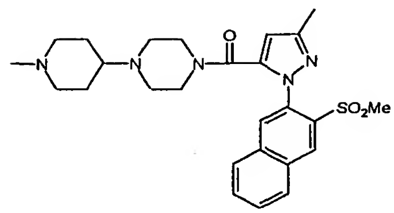
This compound was prepared by the same methodology described for Example 59 with for 3'-(N-tert-Boc-aminomethyl)-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 511.

Example 69.



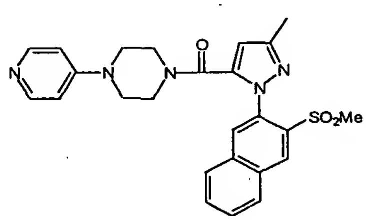
This compound was prepared by the same methodology described for Example 59 with for 1-(4-Aminophenyl)-4-methylpiperazine hydrochloride substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 504.

Example 70.



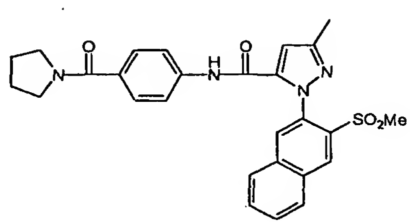
This compound was prepared by the same methodology described for Example 59 with for 1-(N-methylpiperidin-4-yl)-piperazine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 496.

Example 71.



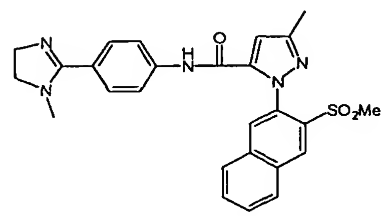
This compound was prepared by the same methodology described for Example 59 with for 1-(4-pyridyl)-piperazine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 476.

Example 72.



This compound was prepared by the same methodology described for Example 59 with for 4-(N-pyrrolidinylcarbonyl)-aniline substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 503.

Example 73.



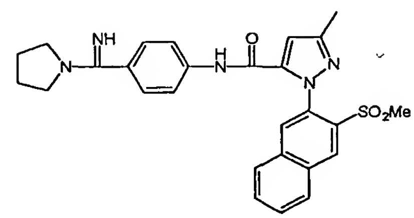
Step 1. The synthesis of 3-methyl-1-(3-methylsulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid was the same as that described in Step 2 of Example 59.

Step 2. The above-prepared acid (200 mg, 0.61 mmol), 4-aminobenzonitrile (108 mg, 0.91 mmol) and DMAP (10 mg) were dissolved in 6 mL pyridine. The solution was stirred at 0°C. To it was added $POCl_3$ (170 μL, 1.8 mmol). The mixture was stirred for 1 hour. The reaction was then quenched with ice chips. It was diluted with EtOAc. The organic phase was washed with brine (X2). It was dried, concentrated and purified with flash column to afford the coupling product (250 mg, 95%). Rf 0.20 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 431.

Step 3. The above-prepared nitrile (70 mg, 0.16 mmol) was dissolved in 6 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached (indicated by a blown-up balloon attached on the top of the reaction flask). The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 463. The solvent was removed in vacuuo. The residue was pumped to dryness. The solid was dissolved in 6 mL dry methanol. To it was added anhydrous N-methylethylenediamine (0.5 mL). The mixture was refluxed for 1 hour,

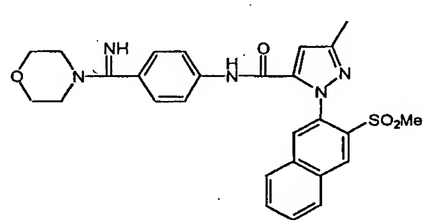
concentrated and loaded on prep HPLC to afford the title compound in 80% yield. ES-MS: $(M+H)^+$ 488.

Example 74.



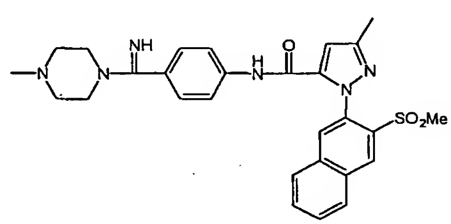
This compound was prepared by the same methodology described for Example 73 with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 502.

Example 75.



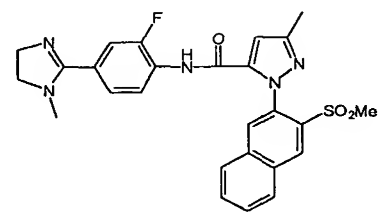
This compound was prepared by the same methodology described for Example 73 with morpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 518.

Example 76.



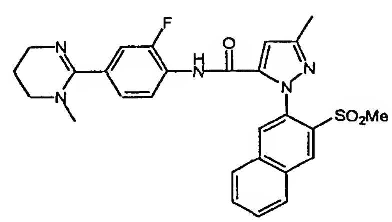
This compound was prepared by the same methodology described for Example 73 with N-methylpiperazine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 531.

Example 77.



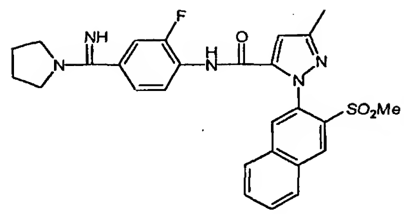
This compound was prepared by the same methodology described for Example 73 with 4-amino-3-fluorobenzonitrile (preparation described in Step 1 of Example 22) substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 506.

Example 78.



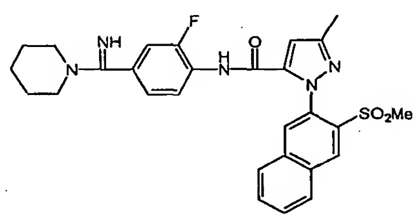
This compound was prepared by the same methodology described for Example 73 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with N-methyl-1,3-propanediamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 520.

Example 79.



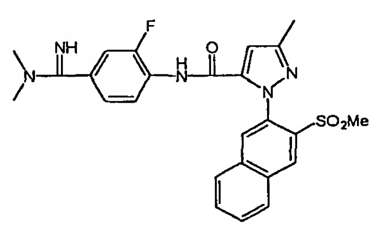
This compound was prepared by the same methodology described for Example 73 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 520.

Example 80.



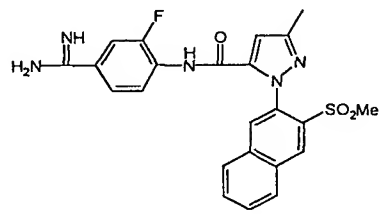
This compound was prepared by the same methodology described for Example 73 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with piperidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 534.

Example 81.



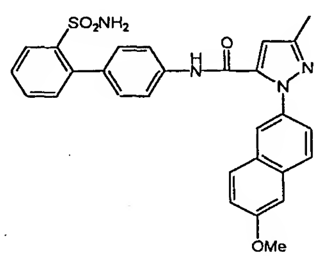
This compound was prepared by the same methodology described for Example 73 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with dimethylamine (2M solution in THF) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 494.

Example 82.



This compound was prepared by the same methodology described for Example 73 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with ammonium acetate substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 466.

Example 83.



Step 1. To a solution of 2-bromo-6-methoxynaphthalene (2.0 g, 8.4 mmol) in 20 mL anhydrous THF at -78°C was added BuLi (1.6M, 7.9 mL, 12.6 mmol) dropwise with a syringe. The mixture was stirred for 30 minutes, then to it was added triisopropyl borane (2.34 mL, 10.1 mmol) dropwise. The dry ice bath was removed. The reaction mixture was allowed to warm up to room temperature. After 15 hours, THF was mostly removed in vacuuo. To the residue was added 40 mL 3M HCl. The mixture

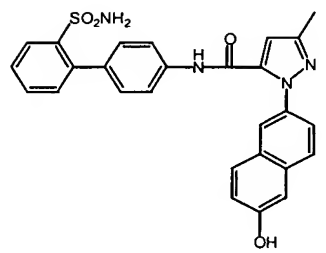
was stirred at room temperature for 8 hours. Ether was used to extract the product (X3). The organic phases were combined, dried, concentrated in vacuuo and pumped to dryness to afford 6-methoxy-2-naphthylboronic acid (75% yield) as a white solid. Rf 0.34 (1:1 EtOAc: hexane).

Step 2. To a solution of the above-prepared boronic acid (0.84 g, 3.2 mmol) and ethyl 3-methylpyrazole-5-carboxylate (0.49 g, 3.2 mmol) in 20 mL dry DCM were added pyridine (0.77 mL, 9.5 mmol) and anhydrous powder of copper(II) acetate (1.15 g, 6.3 mmol). Some activated molecular sieve powder was added afterwards. The resulting slurry was stirred for 4 days under argon. The mixture was diluted with DCM. It was filtered through celite. The blue filtrate was washed with water (X2), dried, concentrated and purified by flash column to separately afford ethyl 3-methyl-1-(6-methoxy-2-naphthyl)-1H-pyrazole-5-carboxylate [37% yield. Rf 0.80 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 311] and ethyl 5-methyl-1-(6-methoxy-2-naphthyl)-1H-pyrazole-3-carboxylate [25% yield. Rf 0.69 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 311] in a 1.5:1 ratio.

Step 3. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (44 mg, 0.14 mmol) in 1 mL DCM was added trimethylaluminum (2.0M in hexane, 0.35 mL, 0.70 mmol) at room temperature. The mixture was stirred for 30 minutes, and to it was added the above-prepared ethyl 3-methyl-1-(6-methoxy-2-naphthyl)-1H-pyrazole-5-carboxylate (44 mg, 0.14 mmol) in 2 mL DCM. The resulting mixture was stirred overnight. The reaction was quenched using 5 mL saturated Rochelle salt aq solution. The mixture was extracted using DCM (X3). The organic phases were combined, dried, concentrated and subjected on flash column to afford the coupling product in 84% yield (67 mg). Rf 0.41 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 569.

Step 4. The above-prepared compound was placed in 3 mL TFA and stirred at 65 ⊕C for 30 minutes. After evaporation, the residue was dissolved in methanol and purified with prep HPLC to afford the title compound in 95% yield. ES-MS: $(M+H)^+$ 513.

Example 84.



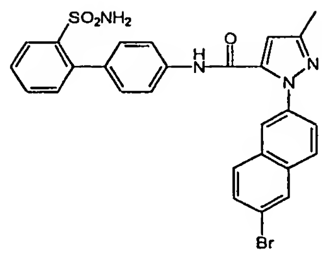
Step 1. The preparation of ethyl 3-methyl-1-(6-methoxy-2-naphthyl)-1H-pyrazole-5-carboxylate was the same as described in Step 2 of Example 83.

Step 2. The above-prepared compound (150 mg, 0.48 mmol) was dissolved in 2 mL DCM. At 0°C, to the stirred solution was added boron tribromide (1.0M in DCM, 0.72 mL, 0.72 mmol). The mixture was stirred overnight at room temperature. It was directly subjected to flash column to afford ethyl 3-methyl-1-(6-hydroxy-2-naphthyl)-1H-pyrazole-5-carboxylate (78 mg, 55%). Rf 0.73 (2:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 297.

Step 3. To a stirred solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (80 mg, 0.26 mmol) in 1 mL DCM was added trimethylaluminum (2.0M in hexane, 0.65 mL, 1.3 mmol) at room temperature. After 30 minutes, to the mixture was added ethyl 3-methyl-1-(6-hydroxy-2-naphthyl)-1H-pyrazole-5-carboxylate (78 mg, 0.26 mmol) in 3 mL DCM. The resulting mixture was stirred 4 hours. The reaction was quenched using 5 mL saturated Rochelle salt aq solution. The mixture was extracted using DCM (X3). The organic phases were combined, dried, concentrated and purified with flash column to afford the coupling product in 65% yield. Rf 0.32 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 555.

Step 4. The above-prepared compound was placed in 3 mL TFA and stirred at 70°C for 30 minutes. After evaporation, the residue was dissolved in methanol and purified with prep HPLC to afford the title compound in 95% yield. ES-MS: $(M+H)^+$ 499.

Example 85.



Step 1. A mixture of 6-bromo-2-naphthoic acid (1.11 g, 4.4 mmol) and 2 mL thionyl chloride was refluxed for overnight. Thionyl chloride was removed in vacuuo. The dry acid chloride was dissolved in 5 mL dioxane. At 0°C to it was added a solution of sodium azide (0.52 g, 8.0 mmol) in 2.5 mL water and 2.5 mL dioxane dropwise. The mixture was stirred for 2 hours. After evaporation in vacuuo to remove the solvent, the residue was dissolved in EtOAc, washed with brine, dried, concentrated in vacuuo to give the azidoketone (1.22 g, 99%). Rf 0.88 (1:1 EtOAc: hexane).

Step 2. The above-prepared compound was dissolved in 20 mL DMF. To it was added 10 mL water. The mixture was refluxed overnight. It was diluted with 500 mL EtOAc, washed with brine (X2), dried, concentrated in vacuuo to afford 6-bromo-2-naphthylamine (1.2 g, 99%). Rf 0.73 (1:1 EtOAc: hexane), ES-MS: $(M+H)^+$ 222, 224 (Br pattern).

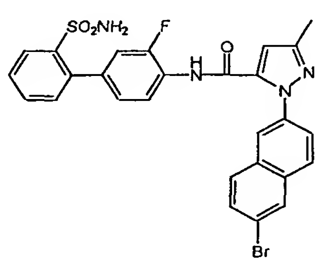
Step 3. The above-prepared compound (1.2 g, 5.4 mmol) was placed in 6 mL concentrate HCl. At 0°C to it was added a solution of sodium nitrite (0.37 g, 5.4 mmol) in 2 mL water dropwise. The mixture was stirred for 30 minutes. At 0°C to the mixture was added a solution of $SnCl_2.2H_2O$ (3.66 g, 16.2 mmol) in 6 mL concentrate HCl dropwise. After stirring for 10 minutes, the mixture was placed in a freezer for overnight. The solid was collected on a cold Buchner funnel. It was washed by ice-cold brine (7 mL) and ice-cold hexane (7 mL). The solid cake was transferred into a flask and pumped to dryness. To it were added 30 mL acetic acid, 15 mL THF, and

ethyl 2-N-(methoxy)imino-4-oxopentanoate (1.3 g, 7.0 mmol). The resulting mixture was refluxed for overnight. The solvent was removed in vacuuo. The residue was dissolved in EtOAc, washed with brine (X2), dried, concentrated and purified by flash column to yield ethyl 3-methyl-1-(6-bromo-2-naphthyl)-1H-pyrazole-5-carboxylate (0.64 g, 33%). Rf 0.71 (1:2 EtOAc: hexane). ES-MS: $(M+H)^+$ 359, 361 (Br pattern).

Step 4. To a stirred solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (93 mg, 0.31 mmol) in 1 mL DCM was added trimethylaluminum (2.0M in hexane, 0.70 mL, 1.4 mmol) at room temperature. After 30 minutes, to the mixture was added the above-prepared ethyl ester (100 mg, 0.28 mmol) in 3 mL DCM. The resulting mixture was stirred overnight. The reaction was quenched using 5 mL saturated Rochelle's salt aq solution. The mixture was extracted using DCM (X3). The organic phases were combined, dried, evaporated and purified with flash column to yield the coupling product (146 mg, 85%). Rf 0.44 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 617, 619 (Br pattern).

Step 5. The above-prepared compound was placed in 3 mL TFA and stirred at 65°C for 40 minutes. After evaporation, the residue was dissolved in methanol and purified with prep HPLC to afford the title compound in 95% yield. ES-MS: $(M+H)^+$ 561, 563 (Br pattern).

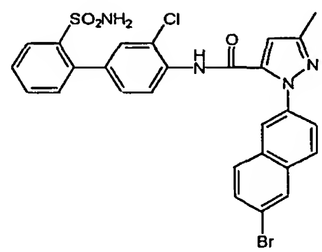
Example 86.



This compound was prepared by the same methodology described for Example 85 with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for

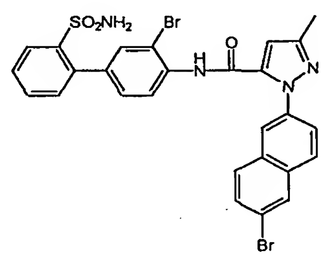
2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 579, 581 (Br pattern).

Example 87.



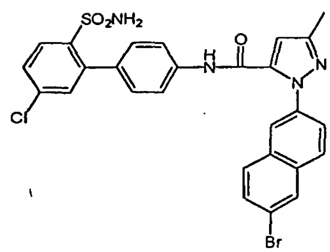
This compound was prepared by the same methodology described for Example 85 with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 595, 597 (BrCl pattern).

Example 88.



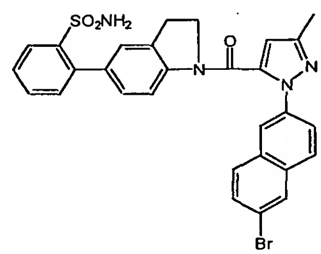
This compound was prepared by the same methodology described for Example 85 with 2'-N-tert-butylaminosulfonyl-3-bromo-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 640, 642, 644 (Br_2 pattern).

Example 89.



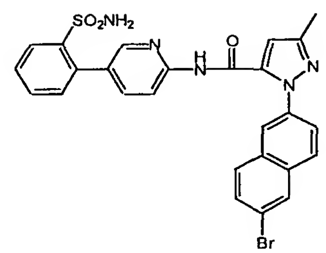
This compound was prepared by the same methodology described for Example 85 with 2'-N-tert-butylaminosulfonyl-5'-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 595, 597 (BrCl pattern).

Example 90.



This compound was prepared by the same methodology described for Example 85 with 5-(2-N-tert-butylaminosulfonyl-1-phenyl)-2,3-dihydroindole substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 587, 589 (Br pattern).

Example 91.



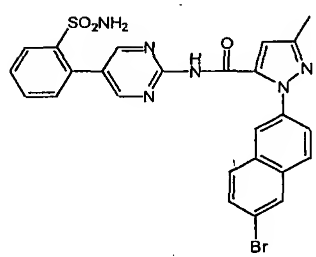
Step 1. The synthesis of ethyl 3-methyl-1-(6-bromo-2-naphthyl)-1H-pyrazole-5-carboxylate was the same as Step 3 of Example 85.

Step 2. The above-prepared ethyl ester (1.0 g, 2.8 mmol) was dissolved in 20 mL methanol. To the solution were added $LiOH.H_2O$ (350 mg, 8.3 mmol) and 10 mL water. The mixture was stirred for overnight and evaporated in vacuuo. The residue was acidified with 1N HCl. It was extracted with EtOAc (X4). The organic phases were combined, dried and concentrated in vacuuo to give 3-methyl-1-(6-bromo-2-naphthyl)-1H-pyrazole-5-carboxylic acid (0.97 g, 100%). ES-MS: $(M+H)^+$ 331, 333 (Br pattern).

Step 3. A mixture of the above-prepared acid (33 mg, 0.10 mmol), 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine (61 mg, 0.20 mmol), DMAP (5 mg) were dissolved in 3 mL pyridine and stirred at 0°C. To it was added $POCl_3$ (55 μL, 0.6 mmol). The mixture was stirred for 2 hours and quenched with ice chips. It was diluted with EtOAc, washed with brine (X2), dried, concentrated and purified with flash column to give the coupling product (34 mg, 55%). Rf 0.35 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 618, 620 (Br pattern).

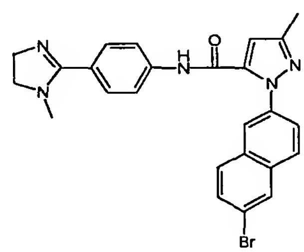
Step 4. The above-prepared compound was placed in 3 mL TFA and stirred at 65°C for 40 minutes. After evaporation, the residue was dissolved in methanol and purified with prep HPLC to afford the title compound in 95% yield. ES-MS: $(M+H)^+$ 562, 564 (Br pattern).

Example 92.



This compound was prepared by the same methodology described for Example 91 with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyrimidine substituted for 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine. ES-MS: $(M+H)^+$ 563, 565 (Br pattern).

Example 93.

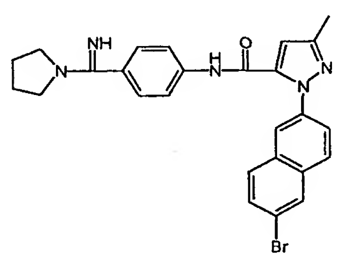


Step 1. The synthesis of 3-methyl-1-(6-bromo-2-naphthyl)-1H-pyrazole-5-carboxylic acid was the same as Step 2 of Example 91.

Step 2. A mixture of the above-prepared acid (970 mg, 2.9 mmol), 4-aminobenzonitrile (700 mg, 5.8 mmol), DMAP (40 mg) were dissolved in 15 mL pyridine and stirred at 0°C. To it was added $POCl_3$ (1.1 mL, 12 mmol). The mixture was stirred for 1 hour and quenched with ice chips. It was diluted with EtOAc, washed with brine (X2), dried, concentrated and purified with flash column to give the coupling product (720 mg, 58%). Rf 0.30 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 431, 433 (Br pattern).

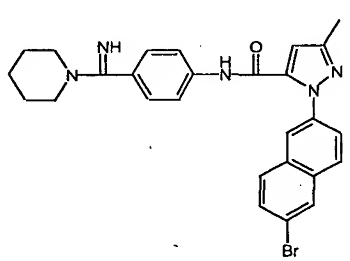
Step 3. The above-prepared nitrile (40 mg, 0.09 mmol) was dissolved in 6 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached. The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 463, 465 (Br pattern). The solvent was removed in vacuuo. The residue was pumped to dryness. The solid was dissolved in 6 mL dry methanol. To it was added anhydrous N-methylethylenediamine (0.5 mL). The mixture was refluxed for 1 hour, concentrated and loaded on prep HPLC to afford the title compound in 85% yield. ES-MS: $(M+H)^+$ 488, 490 (Br pattern).

Example 94.



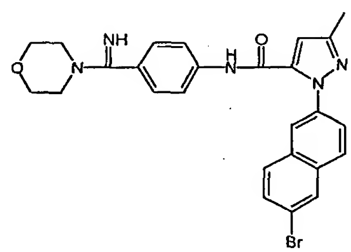
This compound was prepared by the same methodology described for Example 93 with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 502, 504 (Br pattern).

Example 95.



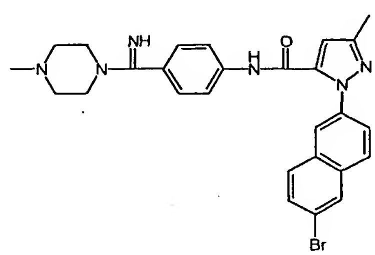
This compound was prepared by the same methodology described for Example 93 with piperidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 516, 518 (Br pattern).

Example 96.



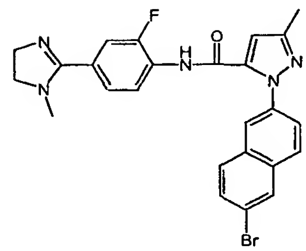
This compound was prepared by the same methodology described for Example 93 with morpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 518, 520 (Br pattern).

Example 97.



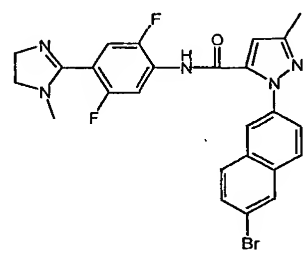
This compound was prepared by the same methodology described for Example 93 with N-methylpiperazine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 531, 533 (Br pattern).

Example 98.



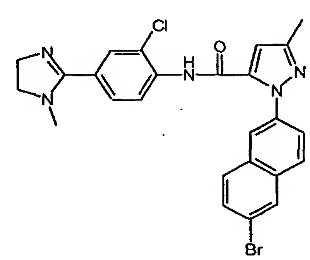
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 506, 508 (Br pattern).

Example 99.



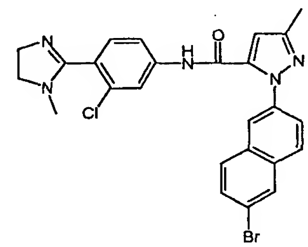
This compound was prepared by the same methodology described for Example 93 with 4-amino-2,5-difluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 524, 526 (Br pattern).

Example 100.



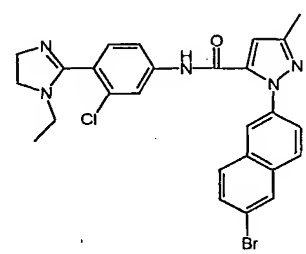
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-chlorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 522, 524 (BrCl pattern).

Example 101.



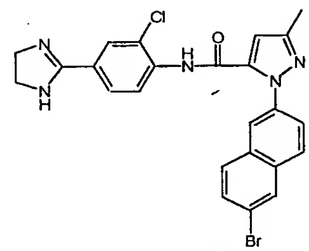
This compound was prepared by the same methodology described for Example 93 with 4-amino-2-chlorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 522, 524 (BrCl pattern).

Example 102.



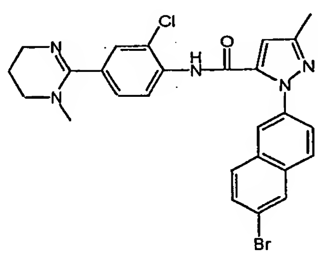
This compound was prepared by the same methodology described for Example 93 with 4-amino-2-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with N-ethyl ethylenediamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 536, 538 (BrCl pattern).

Example 103.



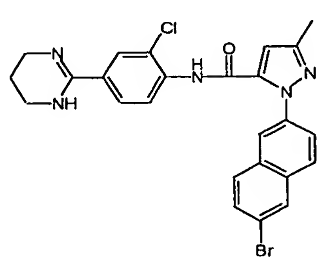
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with ethylenediamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 508, 510 (BrCl pattern).

Example 104.



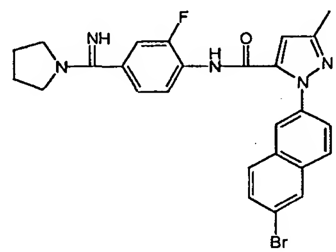
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with N-methyl-1,3-propanediamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 536, 538 (BrCl pattern).

Example 105.



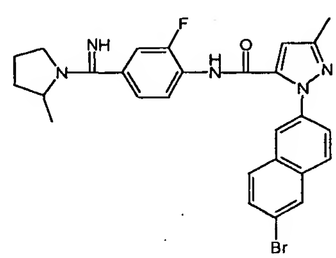
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with 1,3-propanediamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 522, 524 (BrCl pattern).

Example 106.



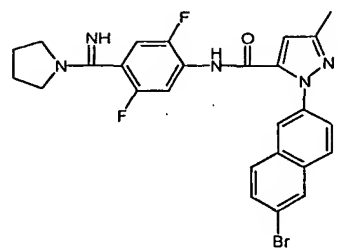
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 520, 522 (Br pattern).

Example 107.



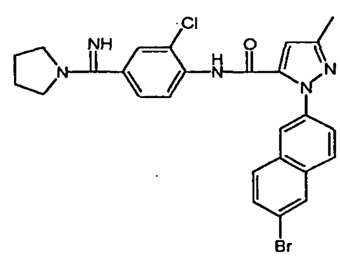
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with 2-methylpyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 534, 536 (Br pattern).

Example 108.



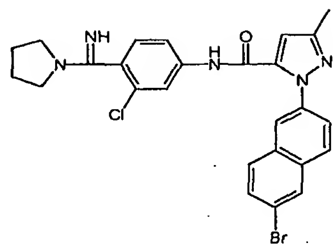
This compound was prepared by the same methodology described for Example 93 with 4-amino-2,5-difluorobenzonitrile substituted for 4-aminobenzonitrile, and with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 538, 540 (Br pattern).

Example 109.



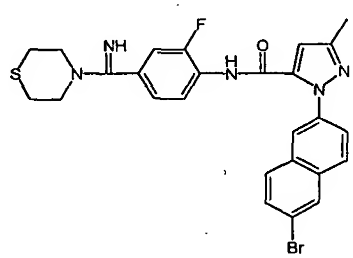
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 536, 538 (BrCl pattern).

Example 110.



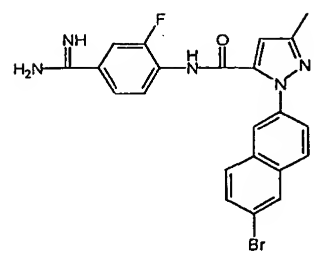
This compound was prepared by the same methodology described for Example 93 with 4-amino-2-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 536, 538 (BrCl pattern).

Example 111.



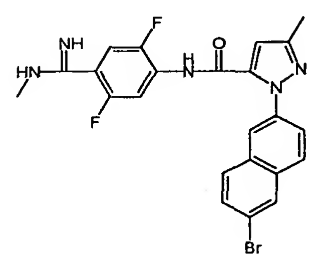
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with thiomorpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 552, 554 (Br pattern).

Example 112.



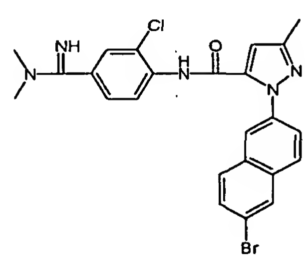
This compound was prepared by the same methodology described for Example 93 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile, and with ammonium acetate substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 466, 468 (Br pattern).

Example 113.



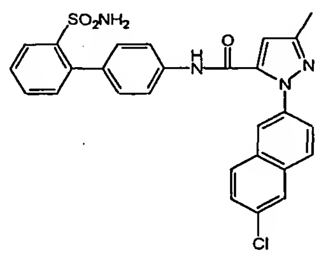
This compound was prepared by the same methodology described for Example 93 with 4-amino-2,5-difluorobenzonitrile substituted for 4-aminobenzonitrile, and with methylamine (2M in methanol) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 498, 500 (Br pattern).

Example 114.



This compound was prepared by the same methodology described for Example 93 with 4-amino-3-chlorobenzonitrile substituted for 4-aminobenzonitrile, and with dimethylamine (2M in THF) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 510, 512 (BrCl pattern).

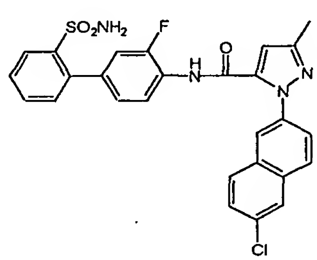
Example 115.



Step 1. To a solution of 6-bromo-2-naphthoic acid (4.4 g, 17.5 mmol) in 50 mL anhydrous DMF were added CuCl (8.7 g, 87.5 mmol) and CuI (0.2 g). The slurry was refluxed for 1 hour. At room temperature it was diluted with 300 mL EtOAc and stirred for 2 hours. It was filtered through celite. The filtrate was evaporated in vacuuo to afford 6-chloro-2-naphthoic acid (2.7 g, 75%). ES-MS: $(M+H)^+$ 207.

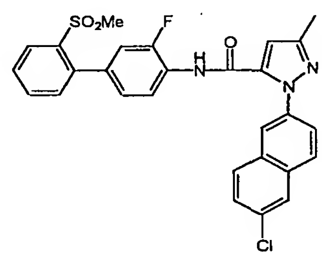
Step 2. The title compound was prepared using the same methodology shown for Example 85, with 6-chloro-2-naphthoic acid substituted for 6-bromo-2-naphthoic acid. ES-MS: $(M+H)^+$ 517.

Example 116.



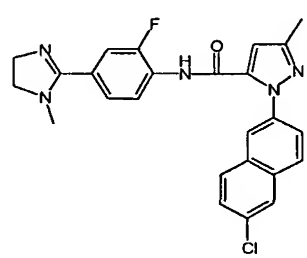
The title compound was prepared using the same methodology shown for Example 115, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl- [1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 535.

Example 117.



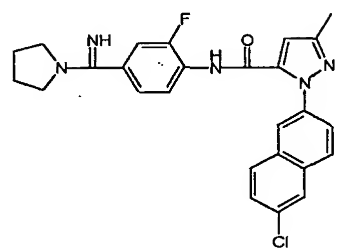
The title compound was prepared using the same methodology shown for Example 115, with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 534.

Example 118.



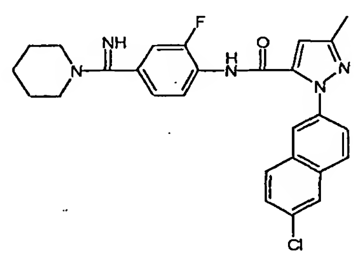
The title compound was prepared using the same methodology shown for Example 98, with 6-chloro-2-naphthoic acid substituted for 6-bromo-2-naphthoic acid. ES-MS: $(M+H)^+$ 462.

Example 119.



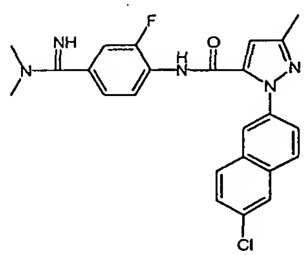
The title compound was prepared using the same methodology shown for Example 106, with 6-chloro-2-naphthoic acid substituted for 6-bromo-2-naphthoic acid. ES-MS: $(M+H)^+$ 476.

Example 120.



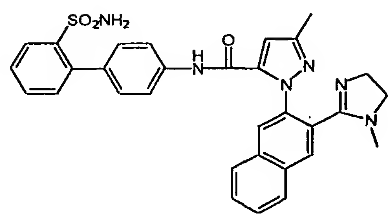
The title compound was prepared using the same methodology shown for Example 119, with piperidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 490.

Example 121.



The title compound was prepared using the same methodology shown for Example 119, with dimethylamine (2M in THF) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 450.

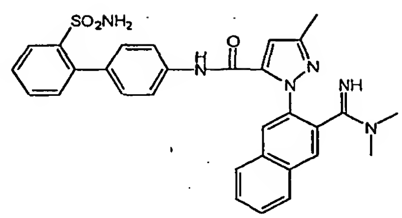
Example 122.



Step 1. The synthesis of 3-methyl-1-(3-cyano-2-naphthyl)-1H-pyrazole-5-(N-(2'-N-tert-butylaminosulfonyl-[1,1']-biphen-4-yl))carboxyamide followed the same procedure shown in Step 3 of Example 34.

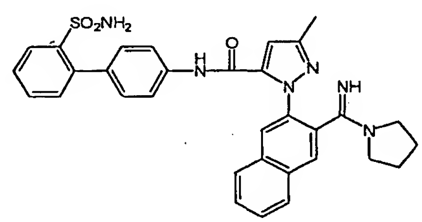
Step 2. To a solution of the above-prepared compound (30 mg) in 10 mL anhydrous ethanol at 0°C was bubbled dry HCl gas via a long needle till saturation reached. The mixture was stirred for overnight. The solvent was removed in vacuuo. The dry residue was dissolved in 5 mL anhydrous methanol. To it was added 0.5 mL N-methylethylenediamine. The mixture was refluxed for 2 hours. ES-MS: $(M+H)^+$ 621. It was concentrated in vacuuo. To the residue was added 3 mL TFA and the mixture was stirred at 70°C for 1 hour. After evaporation, the reaction mixture was subjected on prep HPLC to isolate the title compound (20% yield). ES-MS: $(M+H)^+$ 565.

Example 123.



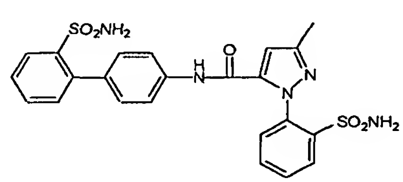
The title compound was prepared using the same methodology shown for Example 122, with dimethylamine (2M in THF) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 553.

Example 124.



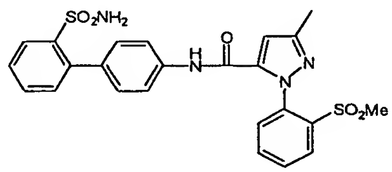
The title compound was prepared using the same methodology shown for Example 122, with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 579.

Example 125.



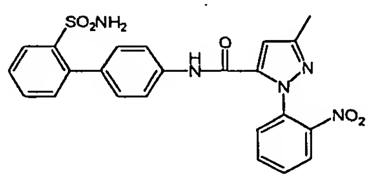
The title compound was prepared using the same methodology shown for Example 1, with 2-N-tert-butylaminosulfonylphenylboronic acid substituted for 2-naphthylboronic acid. ES-MS: $(M+H)^+$ 512.

Example 126.



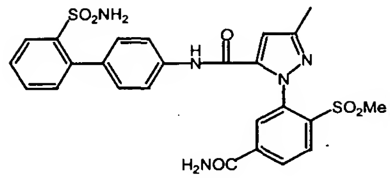
The title compound was prepared using the same methodology shown for Example 1, with 2-methylsulfonylphenylboronic acid substituted for 2-naphthylboronic acid. ES-MS: $(M+H)^+$ 511.

Example 127.



The title compound was prepared using the same methodology shown for Example 52, with commercial 2-nitrophenylhydrazine substituted for 3-carboxyl-2-naphthylhydrazine. ES-MS: $(M+H)^+$ 478.

Example 128.



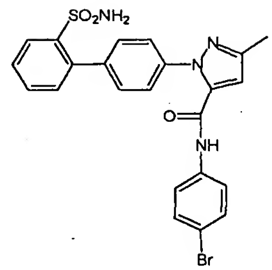
Step 1. 4-methylsulfonyl-3-nitrobenzoic acid (0.90 g, 3.7 mmol) was dissolved in 10 mL ethanol. To it were added hydrazine monohydrate (0.46 mL, 15 mmol) and catalytic amount of 10% Pd/C. The mixture was refluxed for 1.5 hour, diluted with methanol, filtered through celite and concentrated in vacuuo to afford 3-amino-4-methylsulfonylbenzoic acid (>70%). ES-MS: $(M+H)^+$ 216.

Step 2. The above-prepared aniline (2.2 g, 10 mmol) was stirred in 16 mL concentrate HCl in ice bath. To it was dropwise added a cold solution of sodium nitrite (1.1 g, 15 mmol, in 7 mL water). After completion, the mixture was stirred for 30 minutes at 0°C. To it was added dropwise a cold solution of $SnCl_2.2H_2O$ (9.2 g, 40 mmol, in 14 mL concentrate HCl). The mixture was stirred for 30 minutes and filtered through a Buchner funnel. The solid crude hydrazine was collected and dried.

Step 3. The crude hydrazine was dissolved in 40 mL acetic acid. To it were added 20 mL THF and ethyl 2-N-(methoxy)imino-4-oxopentanoate (2.8 g, 15 mmol). The mixture was refluxed for overnight. After removal of the solvent in vacuuo, the reaction mixture residue was dissolved in 800 mL ether. The organic solution was washed with brine (X2), dried, concentrated and purified with flash column to afford ethyl 3-methyl-1-(5-carboxyl-2-methylsulfonylphenyl)-1H-pyrazole-5-carboxylate (2.1 g, 60%). Rf 0.17 (pure EtOAc). ES-MS: $(M+H)^+$ 353.

Step 4. The above-prepared acid (2.1 g, 6.5 mmol) was dissolved in 50 mL dry DMF. To it were added tert-butylamine (1.4 mL, 13 mmol), DIEA (9.2 mL, 52 mmol) and PyBOP (13 g, 26 mmol) in order. The resulting mixture was stirred for overnight at room temperature. DMF was removed in vacuuo. The residue was taken into EtOAc

Example 131.



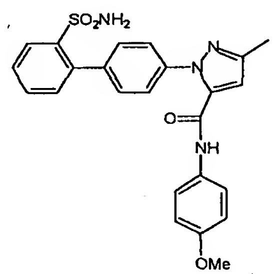
Step 1. 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (1.9 g, 6.2 mmol) was placed in 8 mL concentrate HCl. At 0°C to this stirred mixture was added a cold solution of sodium nitrite (0.43 g, 6.2 mmol in 2 mL water) dropwise. After 30 minutes, to it was added a cold solution of $SnCl_2.2H_2O$ (4.2 g, 18.4 mmol in 8 mL concentrate HCl). The mixture was stirred at 0°C for 1 hour and the solid was collected with a Buchner funnel. The crude solid hydrazine was dried.

Step 2. The above-prepared crude hydrazine was dissolved in 20 mL acetic acid. To it was added 10 mL THF and ethyl 2-N-(methoxy)imino-4-oxopentanoate (0.93 g, 5.0 mmol). The mixture was refluxed for 3 hours. The solvent was removed in vacuuo. The residue was taken into EtOAc, washed with brine, dried, concentrated and purified with flash column to yield ethyl 3-methyl-1-(4-(2-aminosulfonylphenyl)-phenyl)-1H-pyrazole-5-carboxylate (0.95 g, 40%). Rf 0.51 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 386.

Step 3. The above-prepared ethyl ester was dissolved in 20 mL methanol. To it were added $LiOH.H_2O$ (0.31 g, 7.4 mol) and 10 mL water. The mixture was stirred for 3 hours, acidifed till pH 5 with acetic acid, and evaporated in vacuuo. The residue was soaked with acetonitrile and decanted for several times to extract out the organic product. The acetonitrile solutions were combined and evaporated in vacuuo to give yield 3-methyl-1-(4-(2-aminosulfonylphenyl)-phenyl)-1H-pyrazole-5-carboxylic acid (0.81 g, 92%). ES-MS: $(M+H)^+$ 358. It was further purified using prep HPLC.

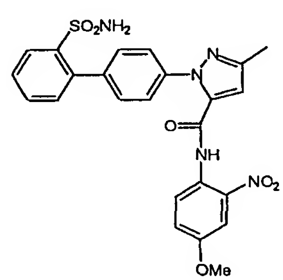
Step 4. The above-prepared acid (20 mg, 0.056 mmol) was dissolved in 1 mL dry DMF. To it were added 4-bromoaniline (10 mg, 0.056 mmol), DIEA (30 μL, 0.17 mmol) and PyBOP (58 mg, 0.12 mmol) in order. The reaction mixture was directly loaded on prep HPLC to yield the title compound in 45% yield. ES-MS: $(M+H)^+$ 511, 513 (Br pattern).

Example 132.



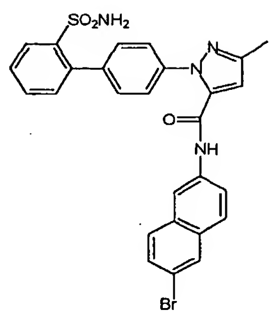
The title compound was prepared using the same methodology shown for Example 131, with 4-methoxyaniline substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 463.

Example 133.



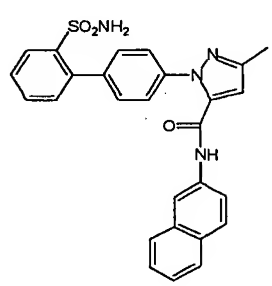
The title compound was prepared using the same methodology shown for Example 131, with 4-methoxy-2-nitroaniline substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 508.

Example 134.



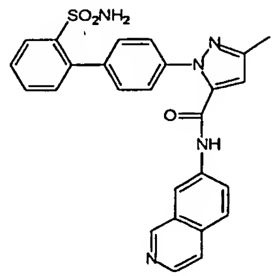
The title compound was prepared using the same methodology shown for Example 131, with 6-bromo-2-naphthylamine substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 562, 564 (Br pattern).

Example 135.



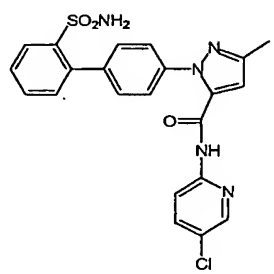
The title compound was prepared using the same methodology shown for Example 131, with 2-naphthylamine substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 483.

Example 136.



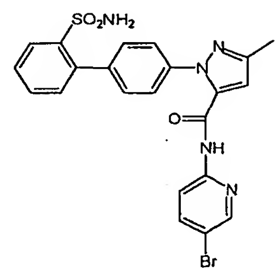
The title compound was prepared using the same methodology shown for Example 131, with 7-aminoisoquinoline substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 484.

Example 137.



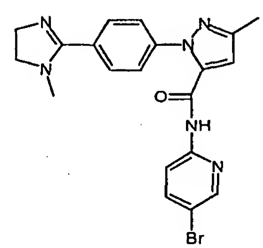
The title compound was prepared using the same methodology shown for Example 131, with 2-amino-5-chloropyridine substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 468.

Example 138.



The title compound was prepared using the same methodology shown for Example 131, with 2-amino-5-bromopyridine substituted for 4-bromoaniline. ES-MS: $(M+H)^+$ 512, 154 (Br pattern).

Example 139.



Step 1. A mixture of 4-cyanophenylhydrazine hydrochloride (5.7 g, 33 mmol), ethyl 2-N-(methoxy)imino-4-oxopentanoate (7.5 g, 40 mmol), 100 mL acetic acid and 50 mL THF was refluxed for 2 hours. The solvent was removed in vacuuo. The residue was taken into 500 mL EtOAc, which was washed with brine, dried and evaporated in vacuuo to afford ethyl 3-methyl-1-(4-cyanophenyl)-1H-pyrazole-5-carboxylate (10 g, 99%). ES-MS: $(M+H)^+$ 256.

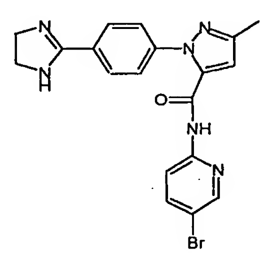
Step 2. The above-prepared ester (10 g) was dissolved in 100 mL THF. To it were added $LiOH.H_2O$ (4.2 g, 100 mmol), 100 mL methanol and 50 mL water. The mixture was stirred for 1 hour. It was acidified to pH 1 with 1N HCl. It was evaporated to remove organic solvent. The residue was extracted with EtOAc (X4). The organic

phases were combined, dried and evaporated to dryness to afford 3-methyl-1-(4-cyanophenyl)-1H-pyrazole-5-carboxylatic acid (95%). ES-MS: $(M+H)^+$ 228.

Step 3. The above-prepared acid (1.4 g, 6.2 mmol) was dissolved in 20 mL pyridine. To it were added 2-amino-5-bromopyridine (2.2 g, 13 mmol) and DMAP (100 mg). At 0°C to this mixture was added $POCl_3$ (2.3 mL, 25 mmol). The reaction was allowed for 1.5 hour and quenched with ice chips. After evaporation in vacuuo, the residue was taken into 300 mL EtOAc, which was washed with brine, dried, evaporated and purified with flash column to yield the coupling product (45%). Rf 0.52 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 382, 384 (Br pattern).

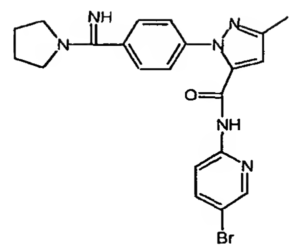
Step 4. To a solution of the above-prepared nitrile (30 mg) in 10 mL anhydrous methanol at 0°C was bubbled dry HCl gas via a long needle till saturation reached. The mixture was stirred for overnight. The solvent was removed in vacuuo. The dry residue was dissolved in 5 mL anhydrous methanol. To it was added 0.5 mL N-methylethylenediamine. The mixture was refluxed for 1 hour. After evaporation, the reaction mixture was subjected on prep HPLC to isolate the title compound (80% yield). ES-MS: $(M+H)^+$ 439, 441 (Br pattern).

<u>Example 140.</u>



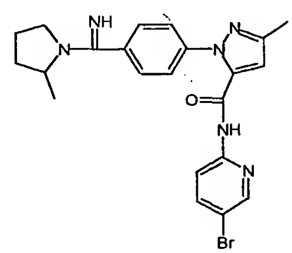
The title compound was prepared using the same methodology shown for Example 139, with ethylenediamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 425, 427 (Br pattern).

Example 141.



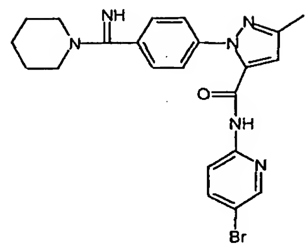
The title compound was prepared using the same methodology shown for Example 139, with pyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 453, 455 (Br pattern).

Example 142.



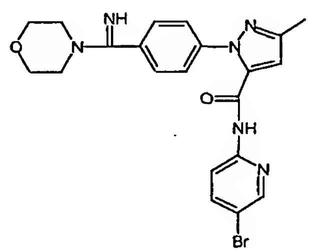
The title compound was prepared using the same methodology shown for Example 139, with 2-methylpyrrolidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 467, 469 (Br pattern).

Example 143.



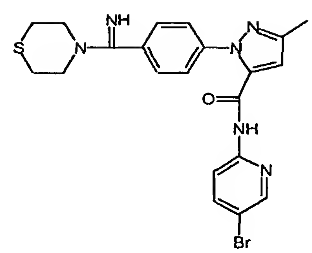
The title compound was prepared using the same methodology shown for Example 139, with piperidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 467, 469 (Br pattern).

Example 144.



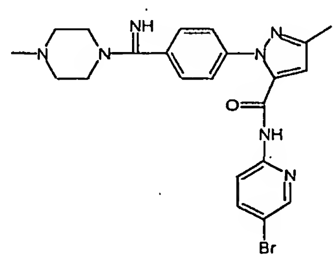
The title compound was prepared using the same methodology shown for Example 139, with morpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 469, 471 (Br pattern).

Example 145.



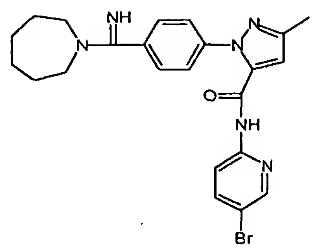
The title compound was prepared using the same methodology shown for Example 139, with thiomorpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 485, 487 (Br pattern).

Example 146.



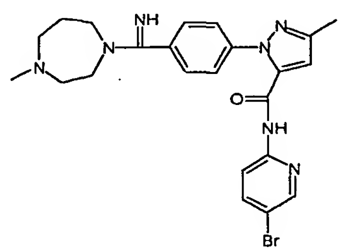
The title compound was prepared using the same methodology shown for Example 139, with N-methylpiperazine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 482, 484 (Br pattern).

Example 147.



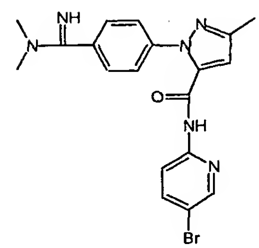
The title compound was prepared using the same methodology shown for Example 139, with hexamethyleneimine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 481, 483 (Br pattern).

Example 148.



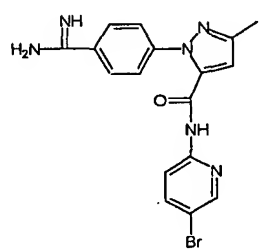
The title compound was prepared using the same methodology shown for Example 139, with 1-methylhomopiperazine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 496, 498 (Br pattern).

Example 149.



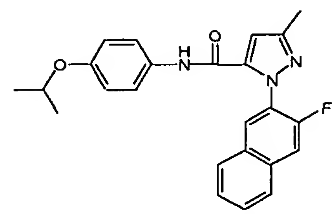
The title compound was prepared using the same methodology shown for Example 139, with dimethylamine (2M in THF) substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 427, 429 (Br pattern).

Example 150.



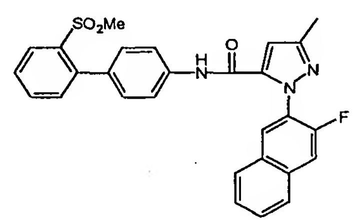
The title compound was prepared using the same methodology shown for Example 139, with ammonium acetate substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 399, 401 (Br pattern).

Example 151



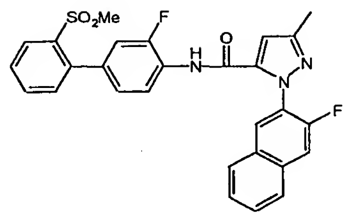
The preparation of 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid was the same as that in Step 1 for Example 4. This acid (39 mg, 0.12 mmol) and 4-isopropoxyaniline (36 mg, 0.24 mmol) were dissolved in 1.4 mL pyridine. To it was added catalytic amount of DMAP. In ice bath, to this stirred mixture was added $POCl_3$ (45 μL, 0.48 mmol). The reaction was allowed for 1 hr and quenched with ice chips. The reaction mixture was diluted with EtOAc. It was washed with brine, dried, evaporated and purified with flash column. Yield 24 mg (50%). Rf 0.53 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 404.

Example 152



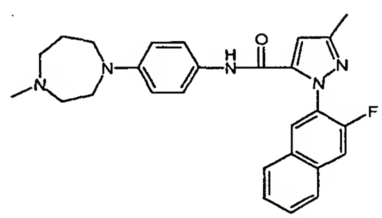
The title compound was prepared by the same technology described for Example 4 with 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine substituted 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the TFA treatment followed. ES-MS: $(M+H)^+$ 500.

Example 153



The title compound was prepared by the same technology described for Example 4 with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine, without the TFA treatment followed. ES-MS: $(M+H)^+$ 518.

Example 154

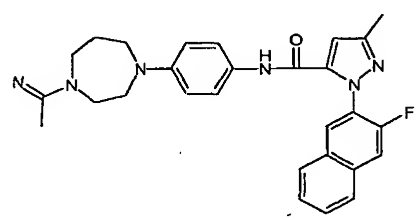


Step 1. The mixture of 1-fluoro-4-nitrobenzene (880 mg, 6.2 mmol), 1-methylhomopiperazine (2.3 mL, 18.6 mmol), Cs_2CO_3 (6.1 g, 18.6 mmol) in 20 mL DMF was stirred at 100°C for 1.5 hr. It was diluted with DCM, filtered to remove the inorganic salts, washed with water, dried, evaporated in vacuuo to afford 1-(4-nitrophenyl)-4-methylhomopiperazine in quantitative yield. ES-MS: $(M+H)^+$ 236.

Step 2. The nitro compound (300 mg) made above was dissolved in 10 mL ethanol. To it was added 10% Pd/C of catalytic amount. The black slurry was stirred under a hydrogen balloon for overnight. The mixture was diluted with EtOAc, filtered through celite, evaporated in vacuuo to afford 1-(4-aminophenyl)-4-methylhomopiperazine in quantitative yield. ES-MS: $(M+H)^+$ 206.

Step 3. 3-Methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (see Step 1, Example 4) (81 mg, 0.3 mmol) and 1-(4-aminophenyl)-4-methylhomopiperazine (205 mg, 1 mmol) were dissolved in 3 mL pyridine. In 0°C to this stirred mixture was added $POCl_3$ (0.18 mL, 2 mmol). The reaction was allowed for 2 hrs and quenched with 1 mL methanol. The mixture was purified using a short silica plug. The crude product was further purified using HPLC. ES-MS: $(M+H)^+$ 458.

<u>Example 155</u>

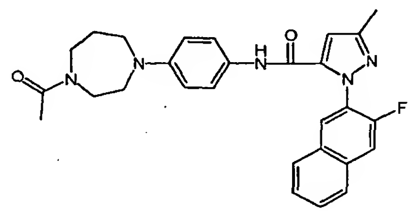


Step 1. 1-Boc-4-(4-nitrophenyl)homopiperazine (prepared with 1-fluoro-4-nitrobenzene, 1-Boc-homopiperazine, Cs_2CO_3 in heated DMF) was dissolved in methanol. To it was added 10% Pd/C. The slurry was stirred under a hydrogen balloon for 2 hrs. It was filtered through celite and evaporated in vacuuo to give 1-(4-aminophenyl)-4-Boc-homopiperazine. ES-MS: $(M+H)^+$ 292.

Step 2. 3-Methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (see Step 1, Example 4) (54 mg, 0.2 mmol) and 1-(4-aminophenyl)-4-Boc-homopiperazine (116 mg, 0.4 mmol) were dissolved in 3 mL pyridine. In 0°C to this stirred mixture was added $POCl_3$ (0.08 mL, 0.8 mmol). The reaction was allowed for 1.5 hrs and quenched with water. The mixture was diluted with EtOAc, washed with water, dried, concentrated in vacuuo to give the coupling amide product. ES-MS: $(M+H)^+$ 544. It was dissolved in 20 mL methanol and to it was bubbled HCl gas till saturation. The mixture was stirred for overnight. It was evaporated in vacuuo to afford 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-[4-(1-homopiperazinyl)phenyl]carboxyamide. ES-MS: $(M+H)^+$ 444.

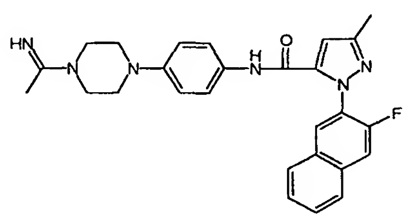
Step 3. The above compound (30 mg, 0.07 mmol) was dissolved in 5 mL dry methanol. To it were added ethyl acetimidate HCl (42 mg, 0.35 mmol) and DIEA (0.06 mL, 0.35 mmol). The mixture was refluxed for overnight and subjected to prep HPLC to afford the title compound. ES-MS: $(M+H)^+$ 485.

Example 156



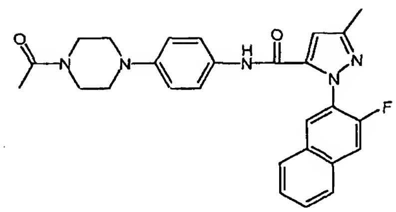
To the mixture of 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-[4-(1-homopiperazinyl)phenyl]carboxyamide (30 mg, 0.07 mmol) in 2 mL pyridine and 2 mL DCM was added acetyl chloride (0.05 mL, 0.7 mmol). The reaction was allowed for 1 hr. The title compound was afforded after prep HPLC purification in quantitative yield. ES-MS: $(M+H)^+$ 486.

Example 157



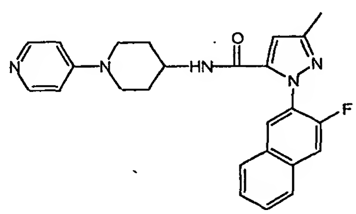
The title compound was prepared using the same methodology described for Example 155, with 1-Boc-piperazine substituted for 1-Boc-homopiperazine. ES-MS: $(M+H)^+$ 471.

Example 158



The title compound was prepared using the same methodology described for Example 156, with 1-Boc-piperazine substituted for 1-Boc-homopiperazine. ES-MS: $(M+H)^+$ 472.

Example 159

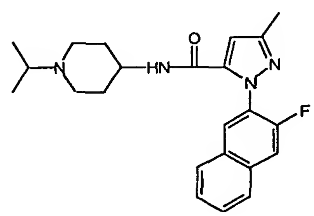


Step 1. The mixture of 4-pyridineboronic acid (0.97 g, 7.8 mmol), 4-Boc-aminopiperidine (3.25 g, 15.8 mmol), $Cu(OAc)_2$ (2.88 g, 15.8 mmol), DMAP (catalytic amount), pyridine (2.5 mL, 32 mmol), 4A activated molecular sieve in 50 mL dry DCM was stirred for over 2 days. It was diluted with DCM, filtered through celite. It was washed with brine and water, dried, filtered through a silica plug, evaporated in vacuuo to give 4-(4-Boc-aminopiperidin-1-yl)pyridine in 90% yield. ES-MS: $(M+H)^+$ 278.

Step 2. The above-prepared compound was dissolved in 50 mL methanol. To it was bubbled HCl gas till saturation in an ice bath. The reaction mixture was stirred for 3 hrs. Evaporated in vacuuo to yield (4-aminopiperidin-1-yl)pyridine. ES-MS: $(M+H)^+$ 178.

Step 3. 3-Methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (see Step 1, Example 4) (48 mg, 0.2 mmol) and 4-(4-aminopiperidin-1-yl)pyridine (95 mg, 0.5 mmol) were dissolved in 1.4 mL pyridine. In 0°C to this stirred mixture was added $POCl_3$ (0.1 mL, 1mmol). The reaction was allowed for 1 hr and quenched with methanol. The mixture was subjected to prep HPLC to isolate the title compound. ES-MS: $(M+H)^+$ 430.

Example 160

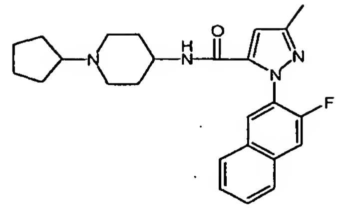


Step 1. 3-Methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (see Step 1, Example 4) (316 mg, 1.2 mmol) and 1-N-Boc-4-aminopiperidine (480 mg, 2.4 mmol) were dissolved in 10 mL pyridine. In 0°C to this stirred mixture was added $POCl_3$ (0.45 mL, 4.8 mmol). The reaction was allowed for 1 hr and quenched with methanol. The mixture was subjected to flash column to isolate the amide in 65% yield (350 mg). Rf 0.10 (1:2 EtOAc: hexane). ES-MS: $(M+H)^+$ 453.

Step 2. The above compound was dissolved in 20 mL dioxane. To it was bubbled HCl gas till saturation. The mixture was stirred for overnight. It was evaporated in vacuuo to yield 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-(4-piperidinyl)carboxyamide. ES-MS: $(M+H)^+$ 353.

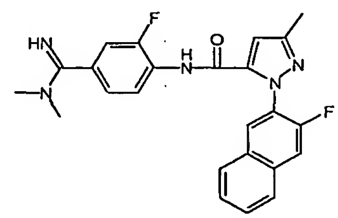
Step 3. The above compound (52 mg, 0.15 mmol) was dissolved in 4 mL methanol. To it were added acetic acid (0.2 mL), acetone (0.22 mL, 3 mmol), $NaBH_3CN$ (38 mg, 0.6 mmol). The mixture was stirred in 50°C bath for 5 hrs. The title compound was isolated with prep HPLC in 80% yield. ES-MS: $(M+H)^+$ 395.

Example 161



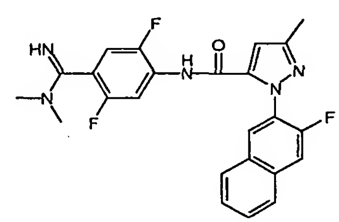
The title compound was prepared using the same methodology shown for Example 160, with cyclopentanone substituted for acetone. ES-MS: $(M+H)^+$ 421.

Example 162



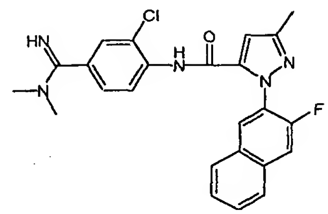
The title compound was prepared using the same methodology described for Example 22, with dimethylamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 434.

Example 163



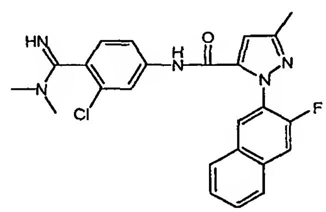
The title compound was prepared using the same methodology described for Example 28, with dimethylamine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 452.

Example 164



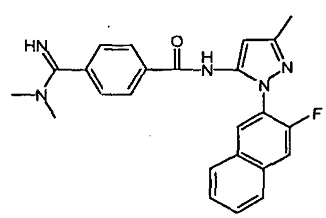
The title compound was prepared using the same methodology described for Example 163, with 4-amino-3-chlorobenzonitrile substituted for 4-amino-2,5-diflourobenzonitrile. ES-MS: $(M+H)^+$ 450.

Example 165



The title compound was prepared using the same methodology described for Example 163, with 4-amino-2-chlorobenzonitrile substituted for 4-amino-2,5-diflourobenzonitrile. ES-MS: $(M+H)^+$ 450.

Example 166



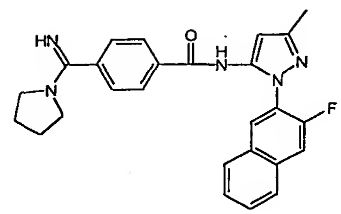
Step 1. 3-Methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (see Step 1, Example 4) (828 mg, 3.1 mmol) was dissolved in 20 mL dry DCM. To it were added

0.05 mL DMF and oxalyl chloride (0.81 mL, 9.3 mL). The mixture was stirred for 2 hrs. It was evaporated in vacuuo. The residue was dissolved in 30 mL dry dioxane. It was chilled in ice bath. To the stirred cold mixture was added dropwise a chilled solution of sodium azide (0.4 g, 6.2 mmol) in 2 mL water and 1 mL dioxane. Reaction was allowed for 1 hr. It was evaporated in vacuuo. The residue was taken into EtOAc and washed with water X2. The organic phase was dried and concentrated in vacuuo. The organic residue was then dissolved in 30 mL DMF. To it was added 15 mL water. The mixture was refluxed for 2.5 hrs. It was concentrated in vacuuo and purified using flash column to give 3-methyl-1-(3-fluoro-2-naphthyl)-5-amino-1H-pyrazole (280 mg, 38% overall). Rf 0.45 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 242.

Step 2. The mixture of above amine (200 mg, 0.83 mmol) and 4-cyanobenzoyl chloride (205 mg, 1.2 mmol) in pyridine (10 mL) with catalytic amount of DMAP was stirred for overnight. The reaction mixture was evaporated in vacuuo and loaded on flash column to give the isolated amide product (50% yield).). Rf 0.45 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 371.

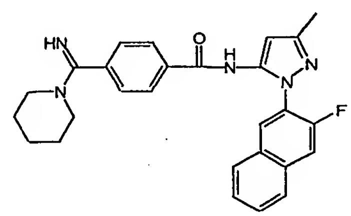
Step 3. The above-prepared nitrile (30 mg, 0.08 mmol) was dissolved in 10 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached (indicated by a blown-up balloon attached on the top of the reaction flask). The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 403. The solvent was removed in vacuuo. The residue was pumped to dryness. The solid was dissolved in 5 mL dry methanol. To it was added dimethylamine (2M in THF, 0.5 mL). The mixture was refluxed for 1 hour, concentrated and loaded on prep HPLC to afford the title compound in 60% yield. ES-MS: $(M+H)^+$ 416.

Example 167



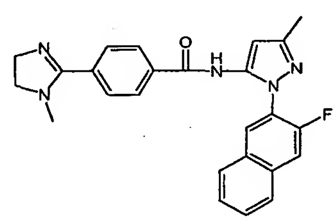
The title compound was prepared using the same methodology described for Example 166, with pyrrolidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 442.

Example 168



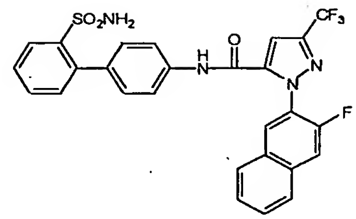
The title compound was prepared using the same methodology described for Example 166, with piperidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 456.

Example 169



The title compound was prepared using the same methodology described for Example 166, with N-methylethylenediamine substituted for dimethylamine. ES-MS: $(M+H)^+$ 428.

Example 170

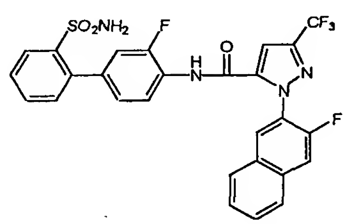


Step 1. 3-fluoro-2-naphthylamine (1.38 g, 8.57 mmol, see Step 2, Example 3) was placed in 20 mL concentrate HCl. The slurry was stirred in ice bath. To it was added dropwise a chilled solution of sodium nitrite (0.71 g, 10.3 mmol) in 4 mL water. After completion, the mixture was stirred for 30 min in ice bath. A chilled solution of $SnCl_2 \cdot 2H_2O$ (4.9 g, 21.6 mmol) in 4 mL concentrate HCl was added dropwise. The mixture was stirred for 30 min. It was chilled and filtered with a Buchner funnel to collect the solid hydrazine. The solid was dried in vacuuo. It was then dissolved in 50 mL glacial acetic acid. To it was added 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (2.18 g, 10.6 mmol). The mixture was refluxed for 2 hrs. The solvent was removed in vacuuo. The residue was taken into DCM. It was washed with water X2, dried, concentrated and subjected to flash column to isolate 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-5-(2-furyl)-1H-pyrazole (60%). Rf 0.52 (1:4 EtOAc: hexane). ES-MS: $(M+H)^+$ 347.

Step 2. The above compound (1.10 g, 3.2 mmol) was dissolved in 30 mL acetone. To it was added a solution of $KMnO_4$ (2.5 g, 16 mmol) in 30 mL water. The mixture was stirred in 60°C bath for 4 hrs. It was cooled and filtered through celite. The celite bed was thoroughly washed with THF. The filtrate was concentrated in vacuuo to remove organic solvent. The aqueous residue was acidified to pH 1 with 2M HCl. It was extracted with EtOAc X4. The organic phases were combined, washed with brine, dried over $MgSO_4$, concentrated in vacuuo to afford isolate 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (55%). ES-MS: $(M+H)^+$ 325.

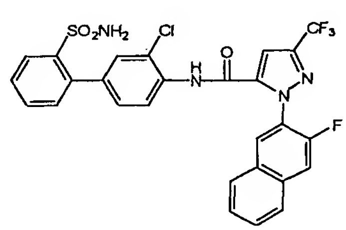
Step 3. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (62 mg, 0.20 mmol) and the above acid (44 mg, 0.14 mmol) in 8 mL pyridine in ice bath was added $POCl_3$ (0.025 mL, 0.27 mmol). The mixture was stirred for 1 hr. Pyridine was removed in vacuuo. The organic residue was taken into EtOAc, which was washed with brine and water. The organic solution was dried and concentrated in vacuuo to yield the crude coupling product (65%). ES-MS: $(M+Na)^+$ 633. It was taken into 10 mL TFA. The mixture was stirred for 5 hrs. It was evaporated in vacuuo and subjected to prep HPLC to give the title compound. ES-MS: $(M+H)^+$ 555.

Example 171



The title compound was prepared using the same methodology described for Example 170, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 573.

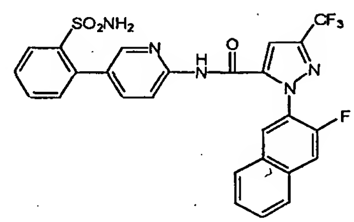
Example 172



The title compound was prepared using the same methodology described for Example 170, with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine

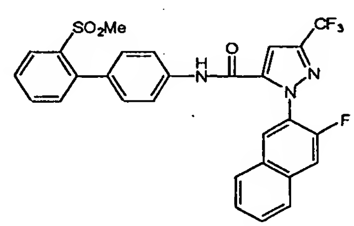
substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 589.

Example 173



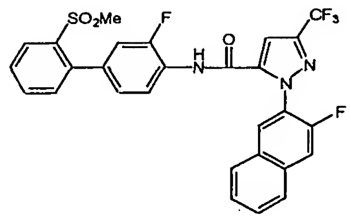
The title compound was prepared using the same methodology described for Example 170, with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 556.

Example 174



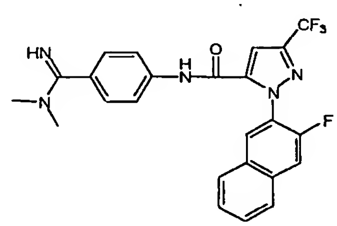
The title compound was prepared using the same methodology described for Example 170, with 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 554.

Example 175



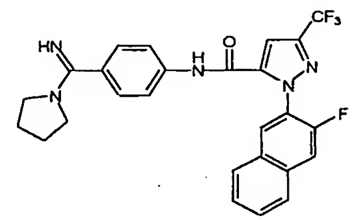
The title compound was prepared using the same methodology described for Example 170, with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 572.

Example 176



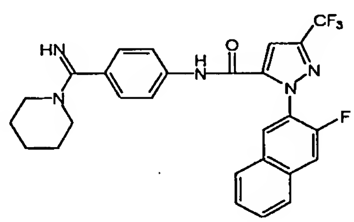
The title compound was prepared using the same methodology described for Example 16, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 470.

Example 177



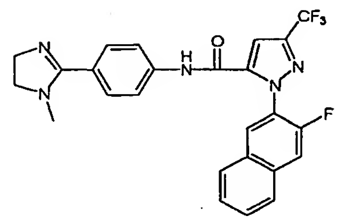
The title compound was prepared using the same methodology described for Example 14, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 496.

Example 178



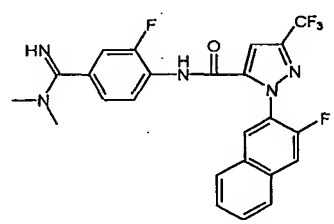
The title compound was prepared using the same methodology described for Example 15, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 510.

Example 179



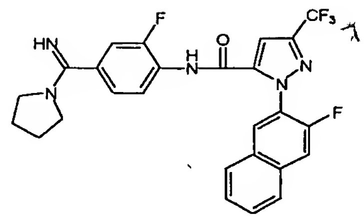
The title compound was prepared using the same methodology described for Example 13, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 482.

Example 180



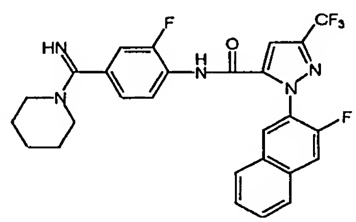
The title compound was prepared using the same methodology described for Example 162, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 488.

Example 181



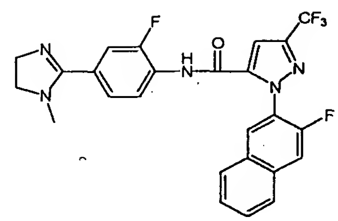
The title compound was prepared using the same methodology described for Example 23, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 514.

Example 182



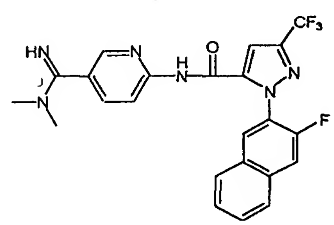
The title compound was prepared using the same methodology described for Example 24, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 528.

Example 183



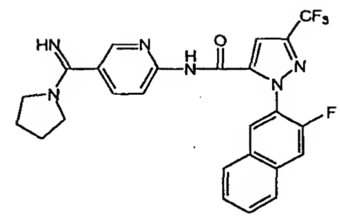
The title compound was prepared using the same methodology described for Example 22, with 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 500.

Example 184



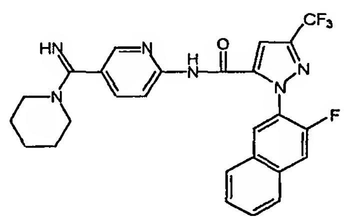
The title compound was prepared using the same methodology described for Example 180, with 2-amino-5-cyanopyridine substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 471.

Example 185



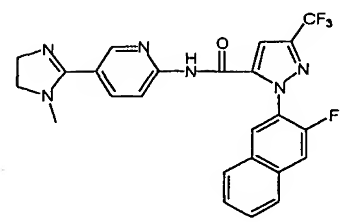
The title compound was prepared using the same methodology described for Example 181, with 2-amino-5-cyanopyridine substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 497.

Example 186



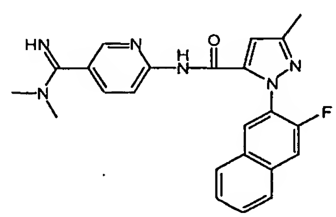
The title compound was prepared using the same methodology described for Example 182, with 2-amino-5-cyanopyridine substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 511.

Example 187



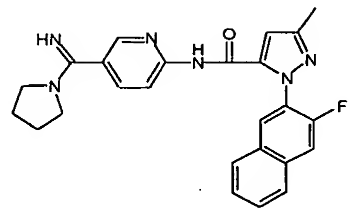
The title compound was prepared using the same methodology described for Example 183, with 2-amino-5-cyanopyridine substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 483.

Example 188



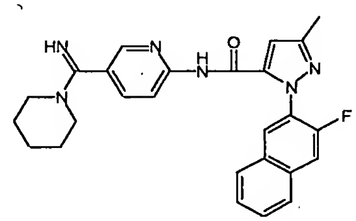
The title compound was prepared using the same methodology described for Example 184, with 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 417.

Example 189



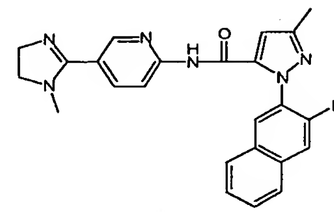
The title compound was prepared using the same methodology described for Example 185, with 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 443.

Example 190



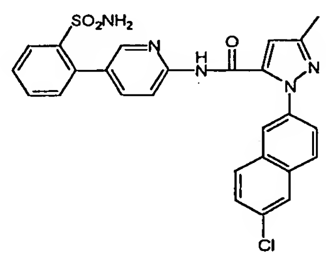
The title compound was prepared using the same methodology described for Example 186 with 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 457.

Example 191



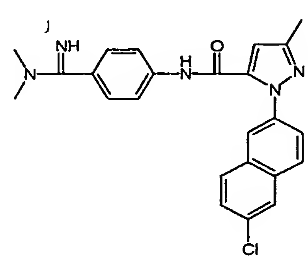
The title compound was prepared using the same methodology described for Example 187, with 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-trifluoromethyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 429.

Example 192



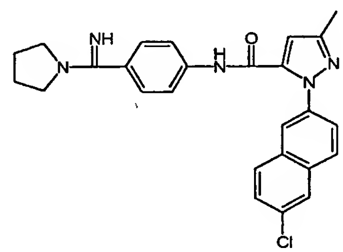
The title compound was prepared using the same methodology shown for Example 91, with 6-chloro-2-naphthoic acid (Step 1, Example 115) substituted for 6-bromo-2-naphthoic acid. ES-MS: $(M+H)^+$ 518.

Example 193



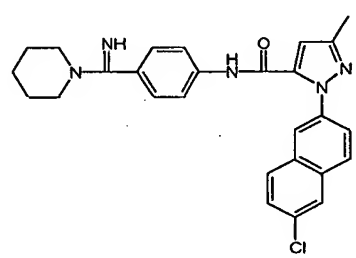
The title compound was prepared using the same methodology shown for Example 121, with 4-aminobenzonitrile substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 432.

Example 194.



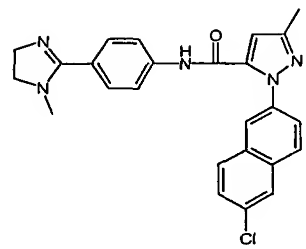
The title compound was prepared using the same methodology shown for Example 119, with 4-aminobenzonitrile substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 458.

Example 195.



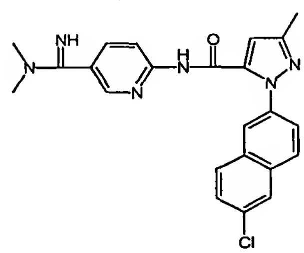
The title compound was prepared using the same methodology shown for Example 120, with 4-aminobenzonitrile substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 472.

Example 196.



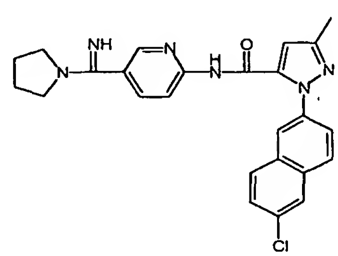
The title compound was prepared using the same methodology shown for Example 118, with 4-aminobenzonitrile substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 444.

Example 197.

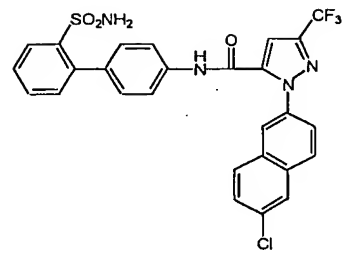


The title compound was prepared using the same methodology shown for Example 121, with 2-amino-5-cyanopyridine substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 433.

Example 198.



Example 201



Step 1. Preparation of 6-chloro-2-naphthylamine. It was prepared using the same methodology shown for Step 1 and Step 2 of Example 85, with 6-chloro-2-naphthoic acid (Step 1, Example 115) substituted for 6-bromo-2-naphthoic acid. ES-MS: $(M+H)^+$ 178.

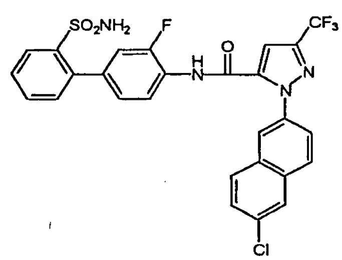
Step 2. The above amine (0.60 g, 3.47 mmol) was placed in 7 mL concentrate HCl. The slurry was stirred in ice bath. To it was added dropwise a chilled solution of sodium nitrite (0.26g, 3.7 mmol) in 2 mL water. After completion, the mixture was stirred for 30 min in ice bath. A chilled solution of $SnCl_2{\cdot}2H_2O$ (1.8 g, 8.2 mmol) in 3 mL concentrate HCl was added dropwise. The mixture was stirred for 30 min. It was chilled and filtered with a Buchner funnel to collect the solid hydrazine. The solid was dried in vacuuo. It was then dissolved in 50 mL glacial acetic acid. To it was added 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (0.70 g, 3.4 mmol). The mixture was refluxed for 2 hrs. The solvent was removed in vacuuo. The residue was taken into chloroform. It was washed with water X2, dried, concentrated and subjected to flash column to isolate 3-trifluoromethyl-1-(6-chloro-2-naphthyl)-5-(2-furyl)-1H-pyrazole (50%). Rf 0.77 (1:2 EtOAc: hexane). ES-MS: $(M+H)^+$ 363.

Step 3. The above compound (150 mg, 0.41 mmol) was dissolved in 5 mL acetone. To it was added a solution of $KMnO_4$ (327 mg, 2.1 mmol) in 2 mL water. The mixture was stirred in 60°C bath for 4 hrs. It was cooled and filtered through celite. The celite bed was thoroughly washed with THF. The filtrate was concentrated in vacuuo to remove organic solvent. The aqueous residue was acidified to pH 1 with 2M HCl. It

was extracted with EtOAc X4. The organic phases were combined, washed with brine, dried over $MgSO_4$, concentrated in vacuuo to afford isolate 3-trifluoromethyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid (120 mg, 86%). ES-MS: $(M+H)^+$ 341.

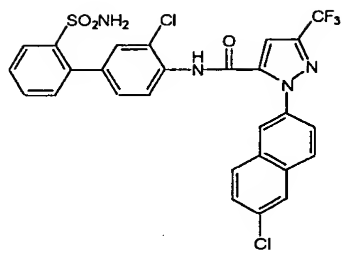
Step 4. To a solution of 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (72 mg, 0.24 mmol) and the above acid (40 mg, 0.12 mmol) in 2 mL pyridine in ice bath was added $POCl_3$ (0.045 mL, 0.48 mmol). The mixture was stirred for 1 hr. Pyridine was removed in vacuuo. The organic residue was taken into EtOAc, which was washed with brine and water. The organic solution was dried and concentrated in vacuuo to yield the crude coupling product (65%). ES-MS: $(M+Na)^+$ 649. It was taken into 5 mL TFA. The mixture was stirred for 5 hrs. It was evaporated in vacuuo and subjected to prep HPLC to give the title compound. ES-MS: $(M+H)^+$ 571.

Example 202



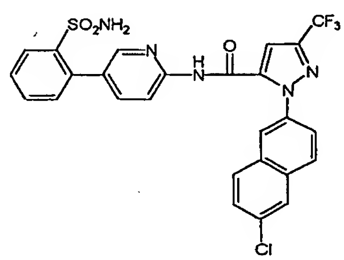
The title compound was prepared using the same methodology described for Example 201, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 589.

Example 203



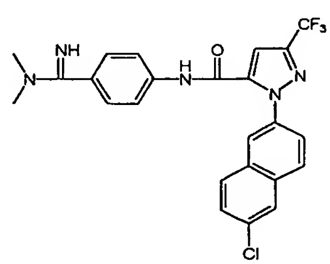
The title compound was prepared using the same methodology described for Example 201, with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 605.

Example 204



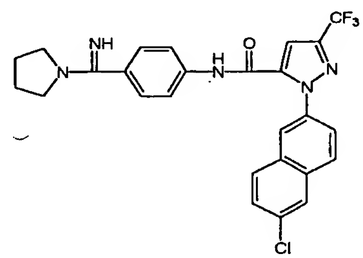
The title compound was prepared using the same methodology described for Example 201, 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 572.

Example 205.



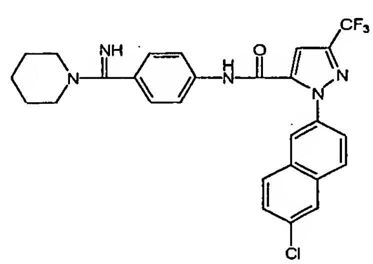
The title compound was prepared using the same methodology shown for Example 193, with 3-trifluoromethyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 486.

Example 206.



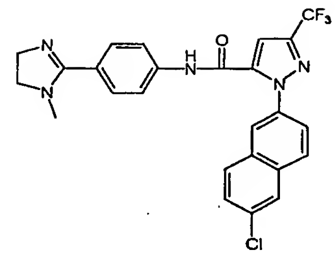
The title compound was prepared using the same methodology shown for Example 194, with 3-trifluoromethyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 512.

Example 207.



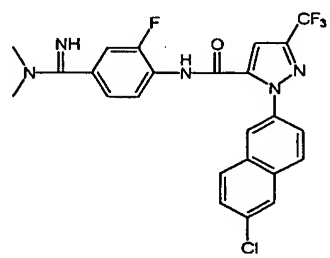
The title compound was prepared using the same methodology shown for Example 195, with 3-trifluoromethyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 526.

Example 208.



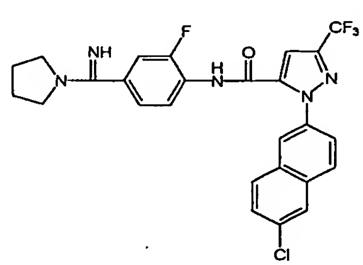
The title compound was prepared using the same methodology shown for Example 196 with 3-trifluoromethyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(6-chloro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 498.

Example 209.



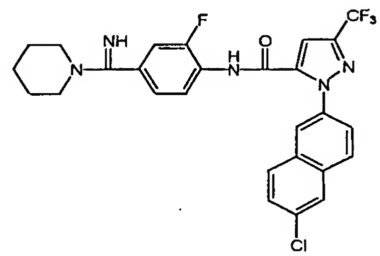
The title compound was prepared using the same methodology shown for Example 205, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 504.

Example 210.



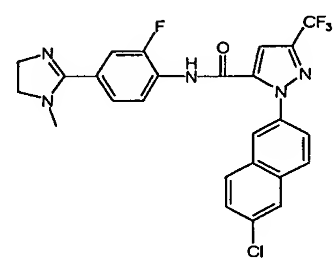
The title compound was prepared using the same methodology shown for Example 206, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 530.

Example 211.



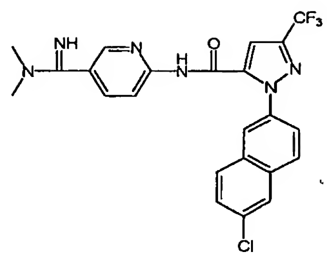
The title compound was prepared using the same methodology shown for Example 207, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 544.

Example 212.



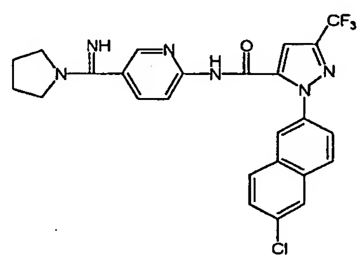
The title compound was prepared using the same methodology shown for Example 208 with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 516.

Example 213.



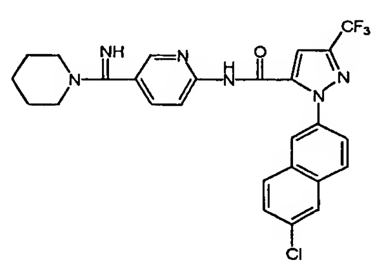
The title compound was prepared using the same methodology shown for Example 205, with 2-amino-5-cyanopyridine substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 487.

Example 214.



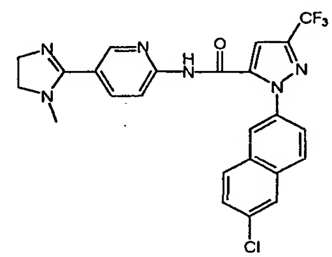
The title compound was prepared using the same methodology shown for Example 206, with 2-amino-5-cyanopyridine substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 513.

Example 215.



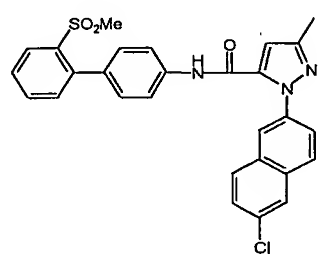
The title compound was prepared using the same methodology shown for Example 207, with 2-amino-5-cyanopyridine substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 527.

Example 216.



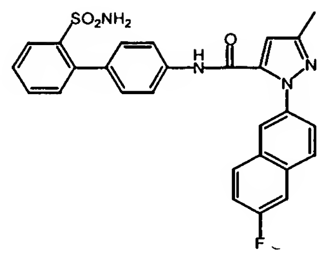
The title compound was prepared using the same methodology shown for Example 208, with 2-amino-5-cyanopyridine substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 499.

Example 217.



The title compound was prepared using the same methodology shown for Example 117, with 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine substituted for 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 516.

Example 218.

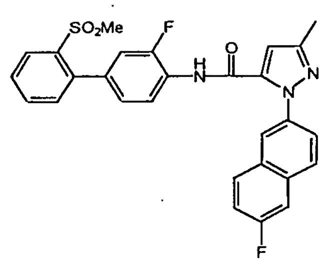


Step 1. 6-Amino-2-naphthoic acid (10.5 g, 56 mmol) was placed in 56 mL concentrate HCl. At 0°C to this vigorously stirred slurry added a cold solution of sodium nitrite (4.6 g, 67 mmol) in 10 mL water. After completion, the mixture was stirred for 30 min in the cold bath. Tetrafluoroboric (48%, 15 mL, 112 mmol) was chilled and added to the reaction mixture. The slurry was stirred in the cold bath for 30 min and filtered through a cold Buchner funnel to collect the solid. The cake was washed with cold tetrafluoroboric acid (10 mL X2). The solid was dried in vacuuo.

Step 2. The above solid was taken into 200 mL toluene. The suspension was refluxed for overnight. Toluene was removed in vacuuo. To residue was taken into 2N HCl. It was extracted with EtOAc X3. The organic phases were combined, washed with brine, dried, concentrated in vacuuo to afford 6-fluoro-2-naphthoic acid (9.5 g, 89%). ES-MS: $(M+Na)^+$ 213.

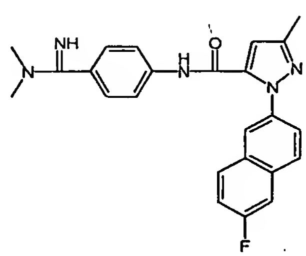
Step 3. The above acid was placed in 100 mL dry DCM with 0.5 mL DMF. To it was added oxalyl chloride (15 mL, 168 mmol) dropwise. The mixture was stirred for overnight. It was concentrated in vacuuo. The dry acid chloride was then dissolved in 200 mL dry dioxane. It was chilled in ice bath and vigorously stirred. To it was dropwise added a cold solution of sodium azide (7.3 g, 112 mmol) in 30 mL water and 30 mL dioxane. The reaction was stirred for 2 hrs. After evaporation in vacuuo, the residue was taken into 300 mL DCM. It was washed with water X3 and then evaporated in vacuuo. The residue was dissolved in 120 mL DMF. To it was added 60 mL water. The mixture was refluxed for 6 hrs. The solvent was removed in vacuuo.

Example 221.



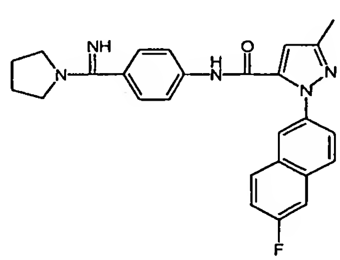
The title compound was prepared using the same methodology shown for Example 218, with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 518.

Example 222



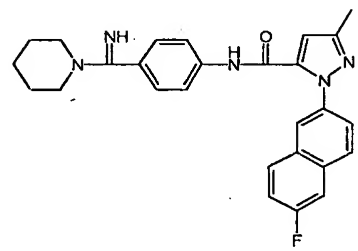
The title compound was prepared using the same methodology shown for Example 193, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 416.

Example 223.



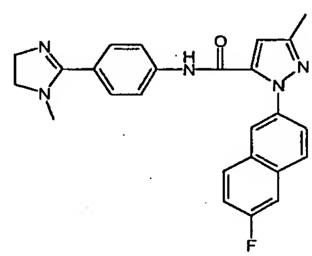
The title compound was prepared using the same methodology shown for Example 194, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 442.

Example 224.



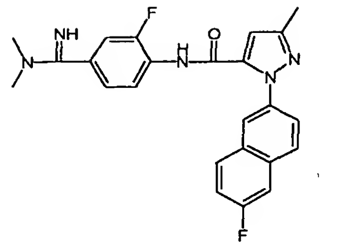
The title compound was prepared using the same methodology shown for Example 195, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 456.

Example 225.



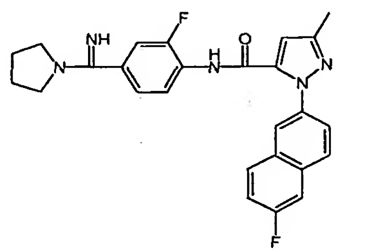
The title compound was prepared using the same methodology shown for Example 196, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 428.

Example 226



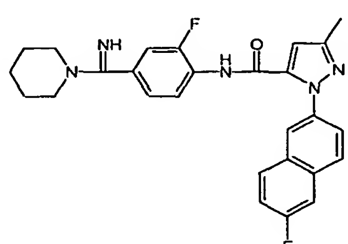
The title compound was prepared using the same methodology shown for Example 121, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 434.

Example 227.



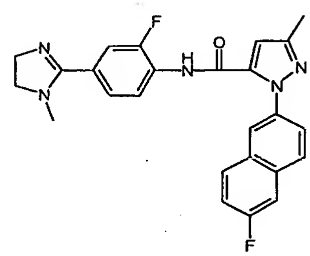
The title compound was prepared using the same methodology shown for Example 119, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 460.

Example 228.



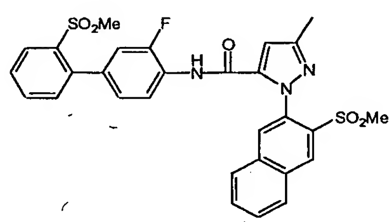
The title compound was prepared using the same methodology shown for Example 120, with 6-fluorò-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 474.

Example 229.



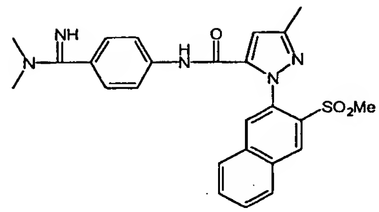
The title compound was prepared using the same methodology shown for Example 118, with 6-fluoro-2-naphthylamine substituted for 6-chloro-2-naphthylamine. ES-MS: $(M+H)^+$ 446.

Example 230



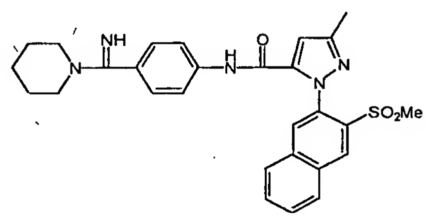
This compound was prepared by the same methodology described for Example 64 with for 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine, without the final TFA treatment. ES-MS: $(M+H)^+$ 578.

Example 231



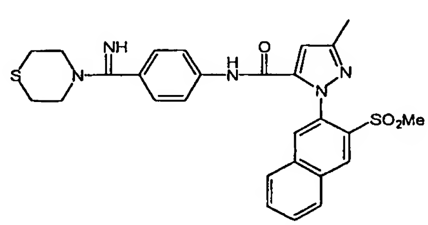
This compound was prepared by the same methodology described for Example 81 with 4-aminobenzonitrile substituted for 4-amino-3-fluorobenzonitrile. ES-MS: $(M+H)^+$ 476.

Example 232



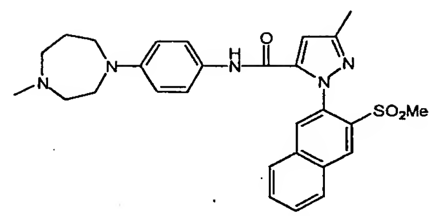
This compound was prepared by the same methodology described for Example 231 with piperidine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 516.

Example 233



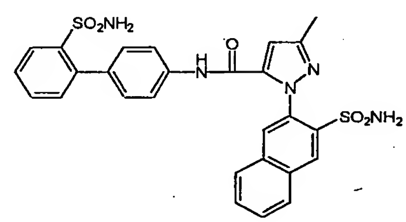
This compound was prepared by the same methodology described for Example 231 with thiomorpholine substituted for N-methylethylenediamine. ES-MS: $(M+H)^+$ 534.

Example 234



This compound was prepared by the same methodology described for Example 69 with 1-(4-aminophenyl)-4-methylhomopiperazine substituted for with 1-(4-aminophenyl)-4-methylpiperazine. ES-MS: $(M+H)^+$ 490.

Example 235



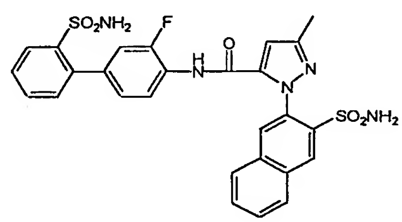
Step 1. Preparation of 3-methyl-1-(3-methylsulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid. It is described in the Step 2 of Example 59.

Step 2. The above acid (1.28 g, 3.88 mmol) was dissolved in 40 mL dry THF and chilled in ice bath. To it was added LiHMDS (1M, 15.5 mL, 15.5 mmol) dropwise. The mixture was stirred for 30 min. Chilled in the ice bath, to it was added Bu_3B (1M, 20 mL, 20 mmol) dropwise. After 2 hrs, the mixture was refluxed for 2.5 hrs. It was cooled and placed in ice bath. To it were added sodium acetate (3.2 g, 39 mmol), water (200 mL) and H_2NOSO_3H (3.5 g, 31 mmol). The mixture was stirred for overnight. It was concentrated in vacuuo. The aqueous residue was acidified to pH 1 with 5N HCl. It was extracted with EtOAc X4. The organic phases were combined,

dried over $MgSO_4$, evaporated in vacuuo to afford 3-methyl-1-(3-aminosulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid (85%). ES-MS: $(M+H)^+$ 332.

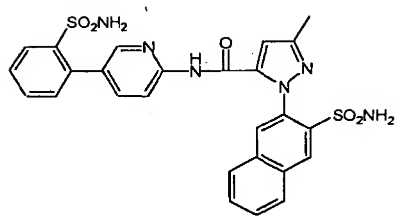
Step 3. The title compound was prepared by the same methodology described for Example 59, with 3-methyl-1-(3-aminosulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-methylsulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid, and also with 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 562.

Example 236



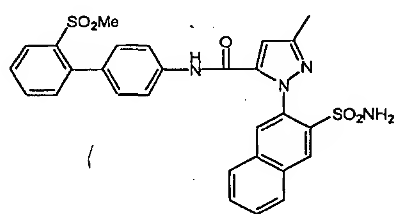
The title compound was prepared by the same methodology described for Example 235, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 580.

Example 237



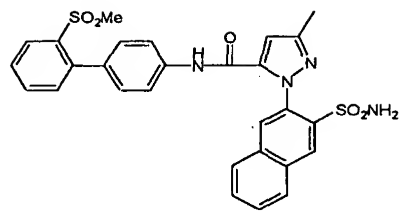
The title compound was prepared by the same methodology described for Example 235, with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 563.

Example 238



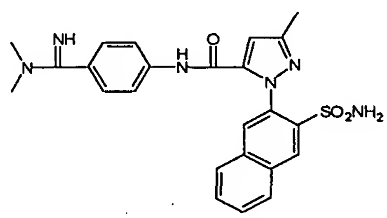
The title compound was prepared by the same methodology described for Example 235, with 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 561.

Example 239



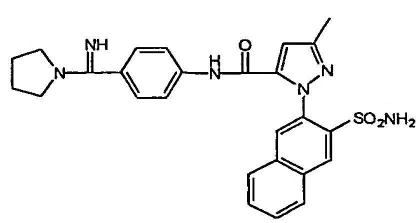
The title compound was prepared by the same methodology described for Example 235, with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 579.

Example 240.



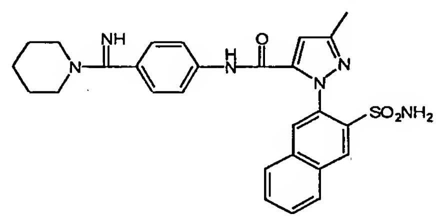
The title compound was prepared using the same methodology shown for Example 16, with 3-methyl-1-(3-aminosulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 477.

Example 241.



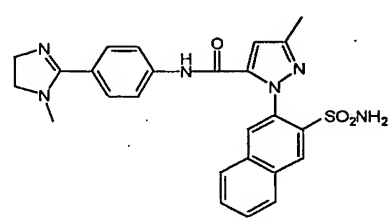
The title compound was prepared using the same methodology shown for Example 14, with 3-methyl-1-(3-aminosulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 503.

Example 242.



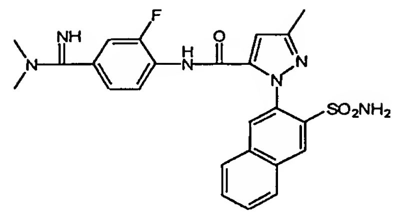
The title compound was prepared using the same methodology shown for Example 15, with 3-methyl-1-(3-aminosulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 517.

Example 243.



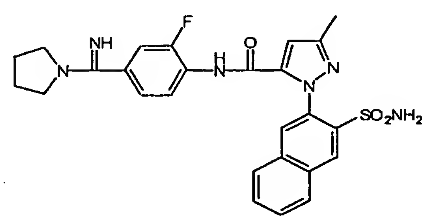
The title compound was prepared using the same methodology shown for Example 13, with 3-methyl-1-(3-aminosulfonyl-2-naphthyl)-1H-pyrazole-5-carboxylic acid substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 489.

Example 244.



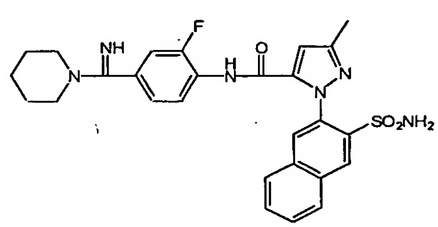
The title compound was prepared using the same methodology shown for Example 240, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 495.

Example 245.



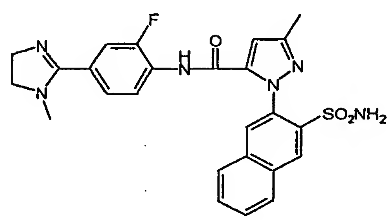
The title compound was prepared using the same methodology shown for Example 241, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 521.

Example 246.



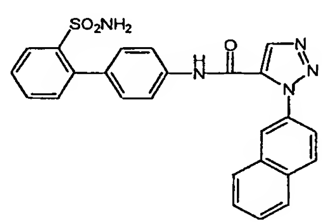
The title compound was prepared using the same methodology shown for Example 242, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 535.

Example 247.



The title compound was prepared using the same methodology shown for Example 243, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 507.

Example 248.



Step 1. 2-Nitronaphthalyene (7.0 g, 40 mmol) was dissolved in 200 mL ethanol. To it was added $SnCl_2{\cdot}2H_2O$ (27.4 g, 121 mmol). The mixture was refluxed for 2.5 hrs. It was concentrated in vacuuo. The residue was taken into DCM, washed with water X3, dried, evaporated in vacuuo to give 2-aminonaphthalene (90%). ES-MS: $(M+H)^+$ 144.

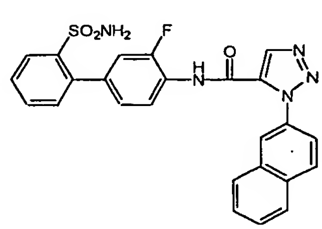
Step 2. The above amine (1.0 g, 7 mmol) was placed in 3 mL TFA. Chilled by ice bath, to it was added sodium nitrite (0.53 g, 7.7 mmol) in small portions. The mixture was stirred in the bath for 45 min. A chilled solution of sodium azide (0.46 g, 7 mmol)

in 1 mL water was added dropwise. The mixture was stirred for 45 min. The reaction was diluted with a cold saturated sodium carbonate aqueous solution. It was extracted with DCM X2. The combined organic phase was dried, evaporated in vacuuo, purified using flash column to give 2-azidonaphthalene (0.69 g, 58%). Rf 0.78 (1:7 EtOAc: hexane).

Step 3.The above compound (0.38 g, 2.2 mmol) was dissolved in 5 mL toluene. To it was added ethyl propiolate (1.1 mL, 11 mmol). The mixture was refluxed for 1.5 hr. It was concentrated in vacuuo and subjected to flash column purification to give a pair of isomers. Ethyl 1-(2-naphthyl)-1,2,3-triazole-5-carboxylate, 200 mg, Rf 0.60 (1:1 EtOAc: hexane), ES-MS: $(M+H)^+$ 268. Ethyl 1-(2-naphthyl)-1,2,3-triazole-4-carboxylate, 400 mg, Rf 0.50 (1:1 EtOAc: hexane), ES-MS: $(M+H)^+$ 268.

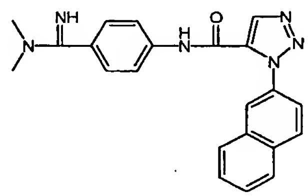
Step 4. The mixture of ethyl 1-(2-naphthyl)-1,2,3-triazole-5-carboxylate (70 mg, 0.26 mmol) and 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (120 mg, 0.39 mmol) was dissolved in 5 mL dry DCM. To it was added trimethylaluminum (2M, 0.7 mL, 1.4 mmol). The mixture was stirred for overnight. It was quenched with aqueous Rochelle's salt solution. It was extracted with DCM X3. The organic phases were combined, dried, evaporated in vacuuo. The residue was taken into 5 mL TFA and stirred for 6 hrs. It was concentrated in vacuuo and purified using HPLC to afford the title compound in about 60% yield. ES-MS: $(M+H)^+$ 470.

Example 249.



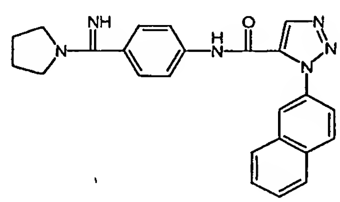
The title compound was prepared using the same methodology shown for Example 248, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 488.

Example 250.



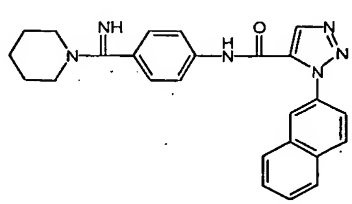
The title compound was prepared using the same methodology shown for Example 16, with ethyl 1-(2-naphthyl)-1,2,3-triazole-5-carboxylate substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 385.

Example 251.



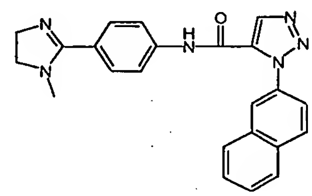
The title compound was prepared using the same methodology shown for Example 250, with pyrrolidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 411.

Example 252.



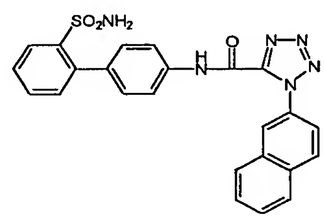
The title compound was prepared using the same methodology shown for Example 250, with piperidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 425.

Example 253.



The title compound was prepared using the same methodology shown for Example 250, with N-methylethylenediamine substituted for dimethylamine. ES-MS: $(M+H)^+$ 397.

Example 254.



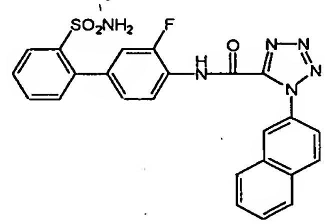
Step 1. 2-Aminonaphthalene (Step 1, Example 248, 1.02 g, 7.1 mmol) was dissolved in 20 mL DCM. To it were added triethylamine (4 mL) and then ethyl oxalyl chloride (0.95 mL, 8.6 mmol) dropwise. The reaction was stirred for 3 hrs. It was concentrated in vacuuo. The residue was taken into DCM, washed with water X2, dried over $MgSO_4$, evaporated in vacuuo to afford the amide in quantitative yield. Rf 0.68 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 244.

Step 2. The above amide (1.46 g, 6 mmol) was dissolved in CCl_4 (30 mL). To it was added a solution of Ph_3P (3.24 g, 12 mmol) in CCl_4 (20 mL). The resulting mixture was refluxed for 22 hrs. It was cooled and filtered through a silica plug. The filtrate

was evaporated in vacuuo to give the iminoyl chloride in high yield (>90%). ES-MS: $(M+H)^+$ 262. This crude iminoyl chloride was dissolved in 40 mL MeCN. To it was added sodium azide (0.47 g, 7.2 mmol). It was stirred for 3 hrs at room temperature. It was concentrated in vacuuo. The residue was taken into EtOAc, washed with water X2, dried, evaporated, purified with flash column to give ethyl 1-(2-naphthyl)-tetrazole-5-carboxylate (70%). Rf 0.69 (1:1 EtOAc: hexane). ES-MS: $(M+H)^+$ 269.

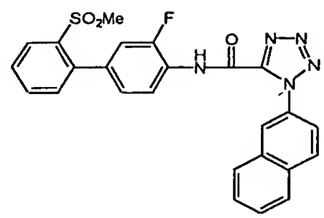
Step 3. The mixture of ethyl 1-(2-naphthyl)-tetrazole-5-carboxylate (50 mg, 0.19 mmol) and 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine (85 mg, 0.28 mmol) was dissolved in 5 mL dry DCM. To it was added trimethylaluminum (2M, 0.5 mL, 1.0 mmol). The mixture was stirred for overnight. It was quenched with aqueous Rochelle's salt solution. It was extracted with DCM X3. The organic phases were combined, dried, evaporated in vacuuo. The residue was taken into 5 mL TFA and stirred for 6 hrs. It was concentrated in vacuuo and purified using HPLC to afford the title compound in about 60% yield. ES-MS: $(M+H)^+$ 471.

Example 255.



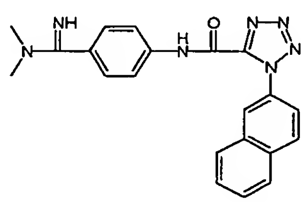
The title compound was prepared using the same methodology shown for Example 254, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 489.

Example 256.



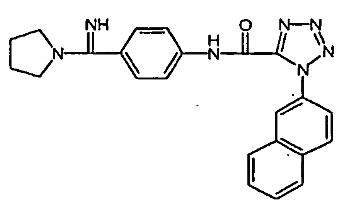
The title compound was prepared using the same methodology shown for Example 254, with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 488.

Example 257.



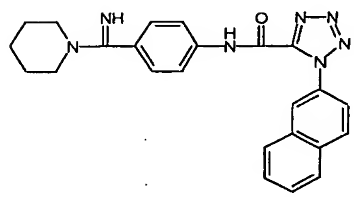
The title compound was prepared using the same methodology shown for Example 16, with ethyl 1-(2-naphthyl)-tetrazole-5-carboxylate substituted for 3-methyl-1-(3-fluoro-2-naphthyl)-1H-pyrazole-5-carboxylic acid. ES-MS: $(M+H)^+$ 386.

Example 258.



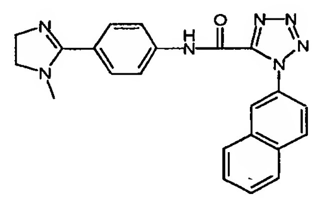
The title compound was prepared using the same methodology shown for Example 257, with pyrrolidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 412.

Example 259.



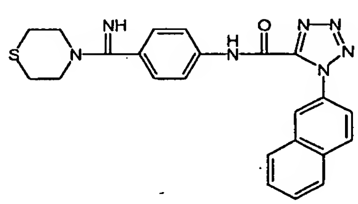
The title compound was prepared using the same methodology shown for Example 257, with piperidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 426.

Example 260.



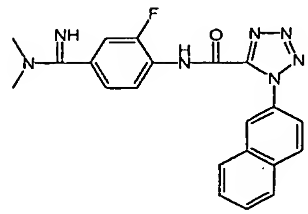
The title compound was prepared using the same methodology shown for Example 257, with N-methylethylenediamine substituted for dimethylamine. ES-MS: $(M+H)^+$ 398.

Example 261.



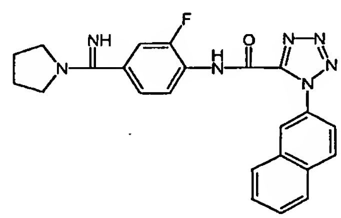
The title compound was prepared using the same methodology shown for Example 257, with thiomorpholine substituted for dimethylamine. ES-MS: $(M+H)^+$ 444.

Example 262.



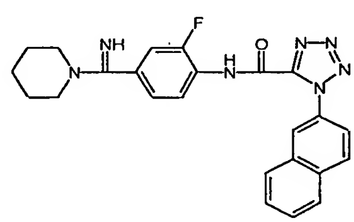
The title compound was prepared using the same methodology shown for Example 257, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 404.

Example 263.



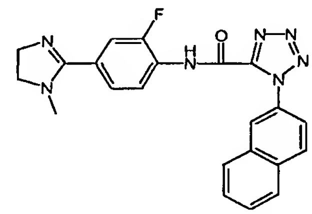
The title compound was prepared using the same methodology shown for Example 258, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 430.

Example 264.



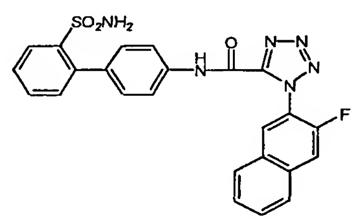
The title compound was prepared using the same methodology shown for Example 259, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 444.

Example 265.



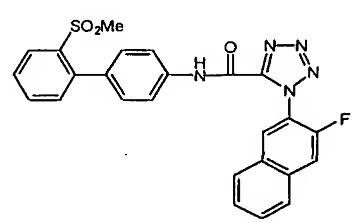
The title compound was prepared using the same methodology shown for Example 260, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzonitrile. ES-MS: $(M+H)^+$ 416.

Example 266.



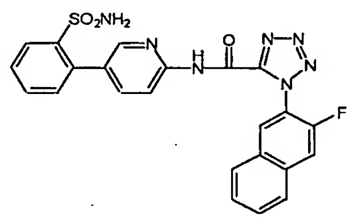
The title compound was prepared using the same methodology shown for Example 254, with 3-fluoro-2-naphthylamine (Step 2, Example 3) substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 489.

Example 267.



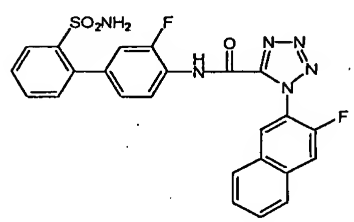
The title compound was prepared using the same methodology shown for Example 266, with 2'-methylsulfonyl-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 488.

Example 268.



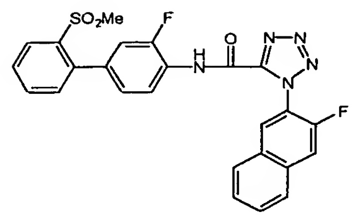
The title compound was prepared using the same methodology shown for Example 266, with 2-amino-5-(2-(N-tert-butylaminosulfonyl)phenyl)pyridine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 490.

Example 269.



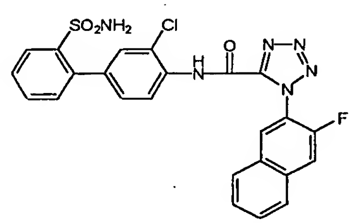
The title compound was prepared using the same methodology shown for Example 266, with 2'-N-tert-butylaminosulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 507.

Example 270.



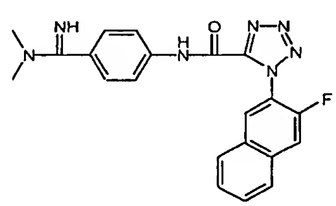
The title compound was prepared using the same methodology shown for Example 266, with 2'-methylsulfonyl-3-fluoro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 506.

Example 271.



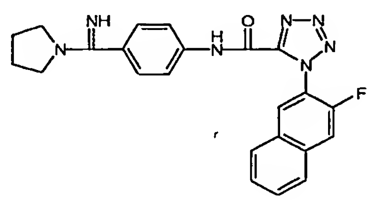
The title compound was prepared using the same methodology shown for Example 266, with 2'-N-tert-butylaminosulfonyl-3-chloro-[1,1']-biphenyl-4-ylamine substituted for 2'-N-tert-butylaminosulfonyl-[1,1']-biphenyl-4-ylamine. ES-MS: $(M+H)^+$ 523.

Example 272.



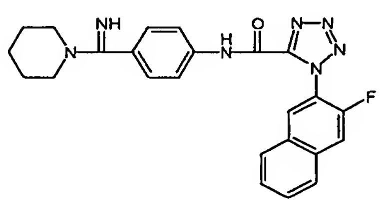
The title compound was prepared using the same methodology shown for Example 257, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 404.

Example 273.



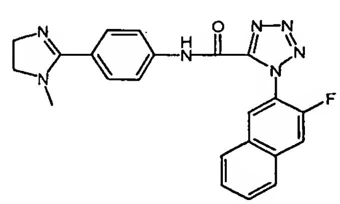
The title compound was prepared using the same methodology shown for Example 258, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 430.

Example 274.



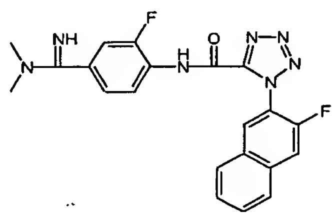
The title compound was prepared using the same methodology shown for Example 259, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 444.

Example 275.



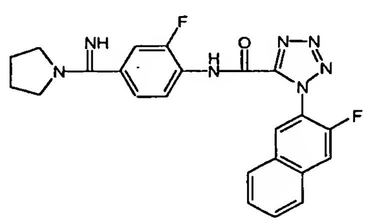
The title compound was prepared using the same methodology shown for Example 260, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 416.

Example 276.



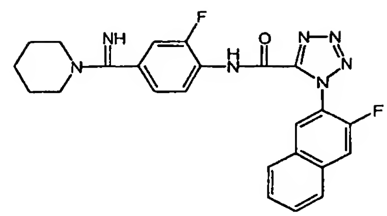
The title compound was prepared using the same methodology shown for Example 262, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 422.

Example 277.



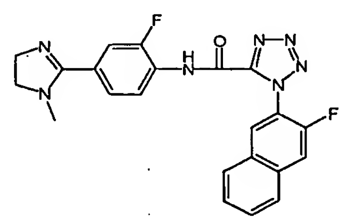
The title compound was prepared using the same methodology shown for Example 263, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 448.

Example 278.



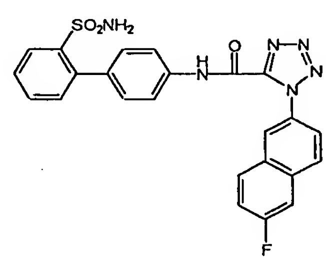
The title compound was prepared using the same methodology shown for Example 264, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 462.

Example 279.



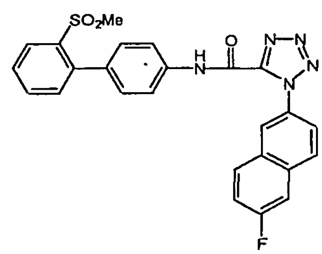
The title compound was prepared using the same methodology shown for Example 265, with 3-fluoro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 434.

Example 280.



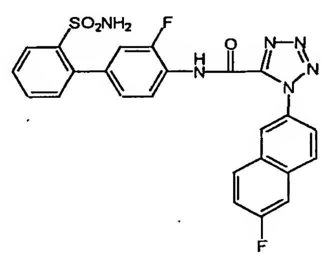
The title compound was prepared using the same methodology shown for Example 254, with 6-fluoro-2-naphthylamine (Step 3, Example 218) substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 489.

Example 281.



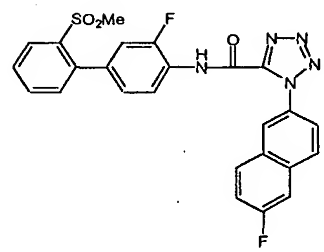
The title compound was prepared using the same methodology shown for Example 267, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 488.

Example 282.



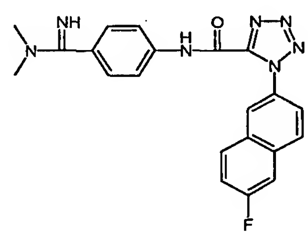
The title compound was prepared using the same methodology shown for Example 269, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 507.

Example 283.



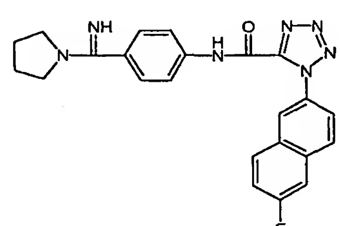
The title compound was prepared using the same methodology shown for Example 270, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 506.

Example 284.



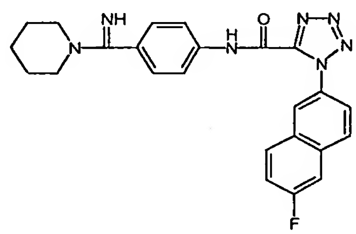
The title compound was prepared using the same methodology shown for Example 272, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 404.

Example 285.



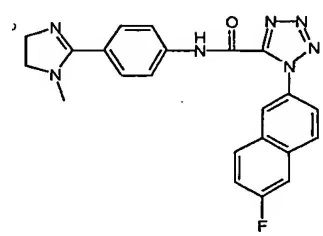
The title compound was prepared using the same methodology shown for Example 273, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 430.

Example 286.



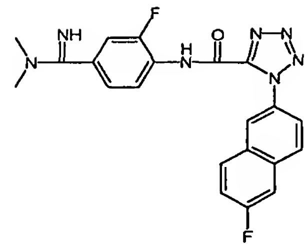
The title compound was prepared using the same methodology shown for Example 274, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 444.

Example 287.



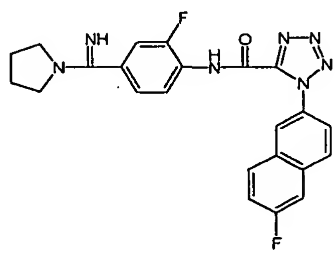
The title compound was prepared using the same methodology shown for Example 275, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 416.

Example 288.



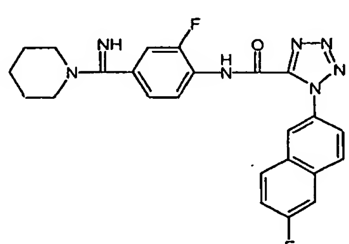
The title compound was prepared using the same methodology shown for Example 276, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 422.

Example 289.



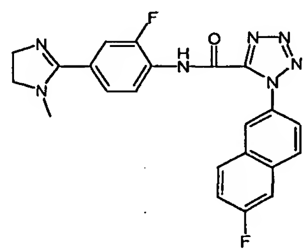
The title compound was prepared using the same methodology shown for Example 277, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 448.

Example 290.



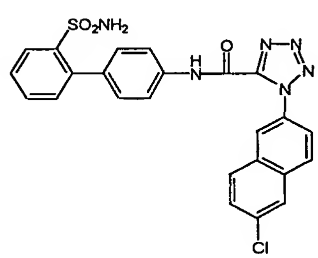
The title compound was prepared using the same methodology shown for Example 278, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 462.

Example 291.



The title compound was prepared using the same methodology shown for Example 279, with 6-fluoro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 434.

Example 292.



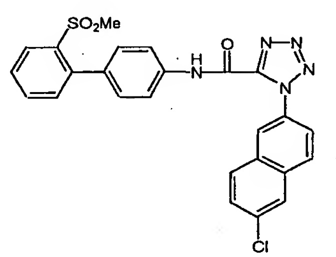
Step 1. Preparation of 6-chloro-2-naphthoic acid is described in Step 1, Example 115.

Step 2. The above acid (6.57 g, 32 mmol) was stirred in 200 mL dry DCM with 0.5 mL DMF. To it was added dropwise oxalyl chloride (8.4 mL, 96 mmol). The reaction was stirred for 2 hrs. It was evaporated in vacuuo to dryness. The residue was taken into 300 mL dry dioxane. It was stirred in ice bath. To this solution was added dropwise a cold solution of sodium azide (4.2 g, 64 mmol) in 15 mL water and 15 mL

dioxane. After completion, the mixture was stirred for 1 hr. It was then concentrated in vacuuo to remove dioxane. The residue was taken into chloroform and washed with water X2. The organic phase was dried, evaporated in vacuuo. It was dissolved in 160 mL DMF. To it was added 80 mL water. The mixture was refluxed for 5 hrs. It was concentrated in vacuuo to remove water and DMF. The residue was taken into 400 mL chloroform, washed with water X2, dried, evaporated in vacuuo to dryness to afford 6-chloro-2-naphthylamine (90%). ES-MS: $(M+H)^+$ 178.

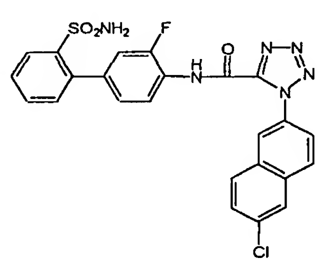
Step 3. The title compound was prepared using the same methodology shown for Example 254, with 6-chloro-2-naphthylamine substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 505.

Example 293.



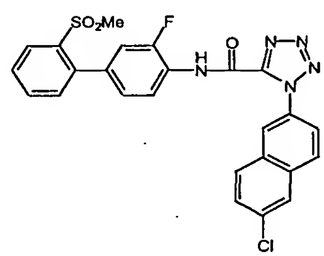
The title compound was prepared using the same methodology shown for Example 267, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 504.

Example 294.



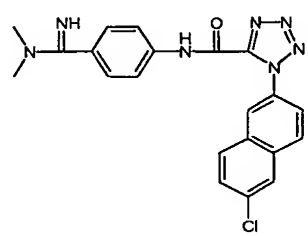
The title compound was prepared using the same methodology shown for Example 269, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 523.

Example 295.



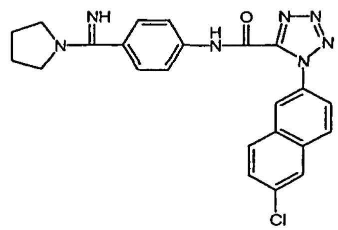
The title compound was prepared using the same methodology shown for Example 270, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 522.

Example 296.



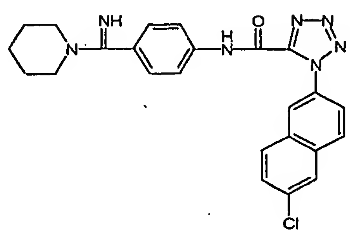
The title compound was prepared using the same methodology shown for Example 272, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 420.

Example 297.



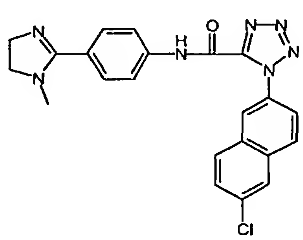
The title compound was prepared using the same methodology shown for Example 273, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 446.

Example 298.



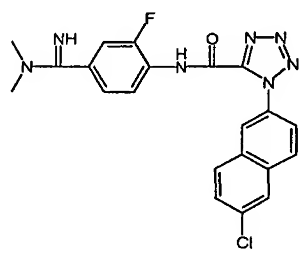
The title compound was prepared using the same methodology shown for Example 274, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 460.

Example 299.



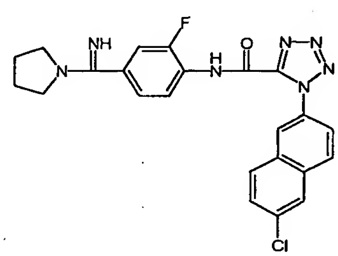
The title compound was prepared using the same methodology shown for Example 275, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 432.

Example 300.



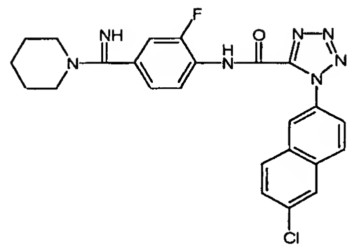
The title compound was prepared using the same methodology shown for Example 276, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 438.

Example 301.



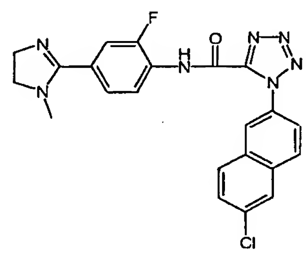
The title compound was prepared using the same methodology shown for Example 277, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 464.

Example 302.



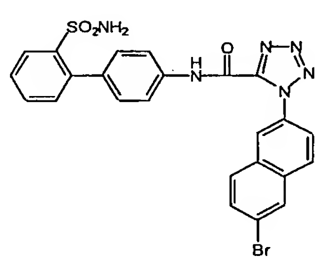
The title compound was prepared using the same methodology shown for Example 278, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 478.

Example 303.



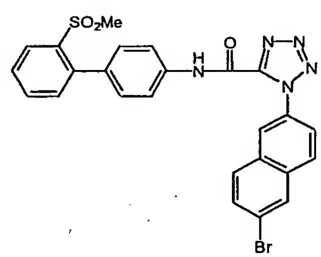
The title compound was prepared using the same methodology shown for Example 279, with 6-chloro-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 450.

Example 304.



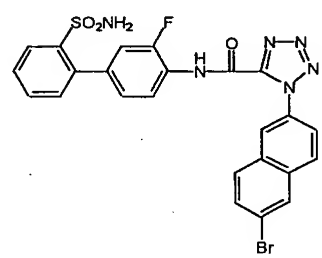
The title compound was prepared using the same methodology shown for Example 254, with 6-bromo-2-naphthylamine (Step 2, Example 85) substituted for 2-naphthylamine. ES-MS: $(M+H)^+$ 549, 551 (Br pattern).

Example 305.



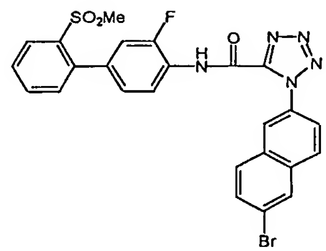
The title compound was prepared using the same methodology shown for Example 267, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 548, 550 (Br pattern).

Example 306.



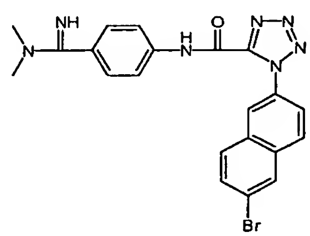
The title compound was prepared using the same methodology shown for Example 269, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 567, 569 (Br pattern).

Example 307.



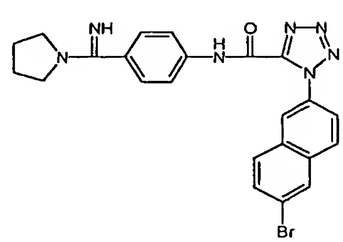
The title compound was prepared using the same methodology shown for Example 270, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 566, 568 (Br pattern).

Example 308.



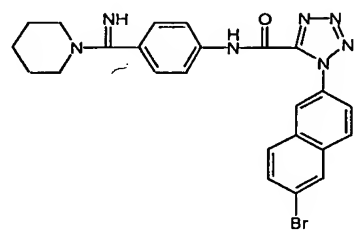
The title compound was prepared using the same methodology shown for Example 272, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 464, 466 (Br pattern).

Example 309.



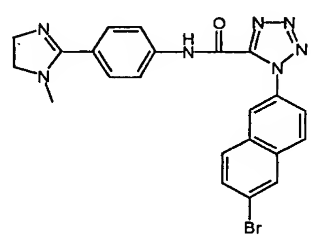
The title compound was prepared using the same methodology shown for Example 273, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 490, 492 (Br pattern).

Example 310.



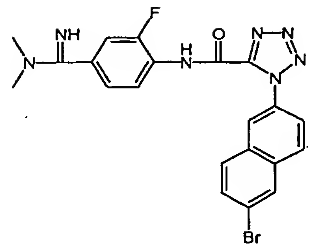
The title compound was prepared using the same methodology shown for Example 274, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 504, 506 (Br pattern).

Example 311.



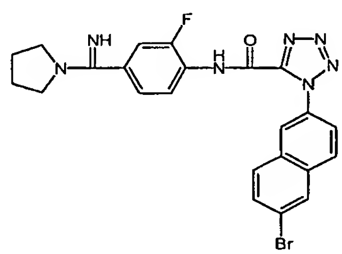
The title compound was prepared using the same methodology shown for Example 275, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 476, 478 (Br pattern).

Example 312.



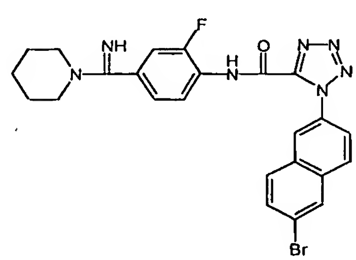
The title compound was prepared using the same methodology shown for Example 276, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 482, 484 (Br pattern).

Example 313.



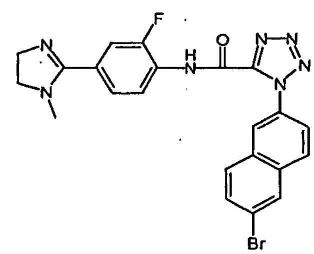
The title compound was prepared using the same methodology shown for Example 277, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 508, 510 (Br pattern).

Example 314.



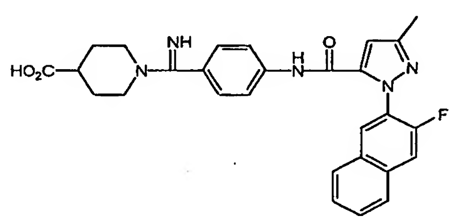
The title compound was prepared using the same methodology shown for Example 278, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 522, 524 (Br pattern).

Example 315.



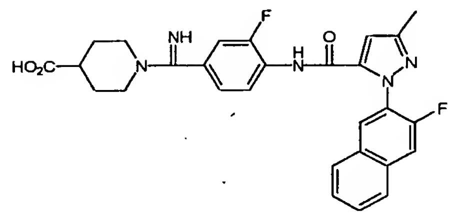
The title compound was prepared using the same methodology shown for Example 279, with 6-bromo-2-naphthylamine substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 494, 496 (Br pattern).

Example 316.



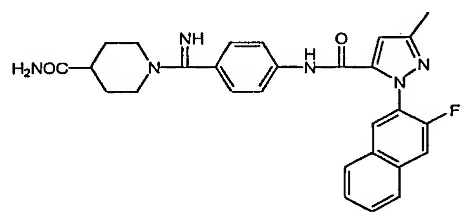
The title compound was prepared using the same methodology shown for Example 15, with isonipecotic acid substituted for piperidine. ES-MS: $(M+H)^+$ 500.

Example 317.



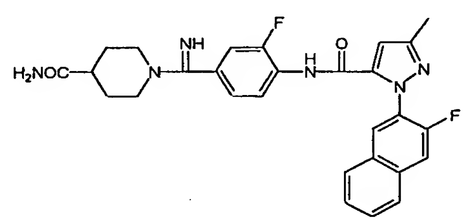
The title compound was prepared using the same methodology shown for Example 24, with isonipecotic acid substituted for piperidine. ES-MS: $(M+H)^+$ 518.

Example 318.



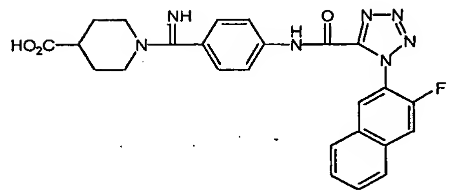
The title compound was prepared using the same methodology shown for Example 15, with isonipecotamide substituted for piperidine. ES-MS: $(M+H)^+$ 499.

Example 319.



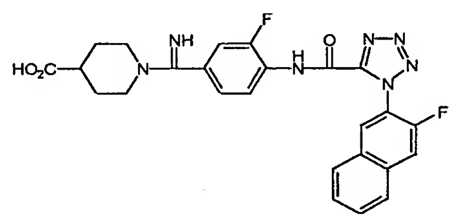
The title compound was prepared using the same methodology shown for Example 24, with isonipecotictamide substituted for piperidine. ES-MS: $(M+H)^+$ 517.

Example 320.



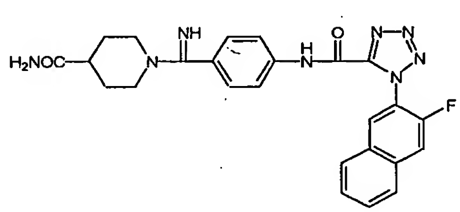
The title compound was prepared using the same methodology shown for Example 274, with isonipecotic acid substituted for piperidine. ES-MS: $(M+H)^+$ 488.

Example 321.



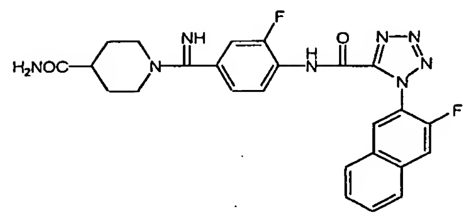
The title compound was prepared using the same methodology shown for Example 278, with isonipecotic acid substituted for piperidine. ES-MS: $(M+H)^+$ 506.

Example 322.



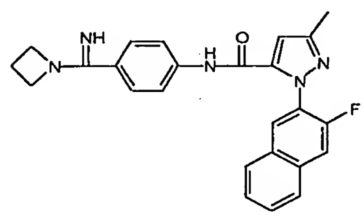
The title compound was prepared using the same methodology shown for Example 274, with isonipecotamide substituted for piperidine. ES-MS: $(M+H)^+$ 487.

Example 323.



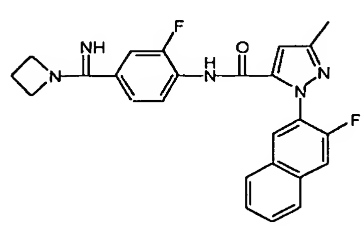
The title compound was prepared using the same methodology shown for Example 278, with isonipecotictamide substituted for piperidine. ES-MS: $(M+H)^+$ 505.

Example 324.



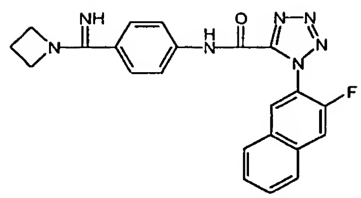
The title compound was prepared using the same methodology shown for Example 14, with azetidine substituted for pyrrolidine. ES-MS: $(M+H)^+$ 428.

Example 325.



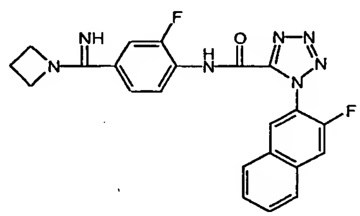
The title compound was prepared using the same methodology shown for Example 23, with azetidine substituted for pyrrolidine. ES-MS: $(M+H)^+$ 446.

Example 326.



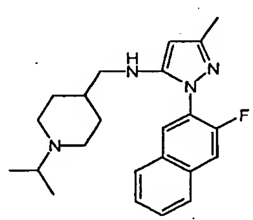
The title compound was prepared using the same methodology shown for Example 273, with azetidine substituted for pyrrolidine. ES-MS: $(M+H)^+$ 416.

Example 327.



The title compound was prepared using the same methodology shown for Example 277, with azetidine substituted for pyrrolidine. ES-MS: $(M+H)^+$ 434.

Example 328.

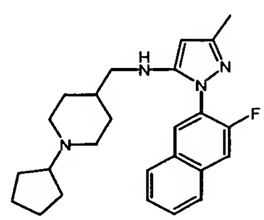


Step 1. Preparation of 3-methyl-1-(3-fluoro-2-naphthyl)-5-amino-1H-pyrazole. It is described in Step 1, Example 166.

Step 2. To a solution of the above amine (200 mg, 0.82 mmol) in 5 mL DMF were added tert-butyl 4-(((methylsulfonyl)oxy)methyl)-1-piperidinecarboxylate (480 mg, 1.6 mmol) and Cs_2CO_3 (0.53 g, 1.6 mmol). The mixture was stirred at 80°C for overnight. The mixture was diluted with 200 mL EtOAc, washed with water X3, dried, concentrated in vacuuo. The residue was then dissolved in dioxane (30 mL). To it was bubbled with HCl gas till saturation. The mixture was stirred for 5 hrs. It was concentrated and purified with prep HPLC to afford 3-methyl-1-(3-fluoro-2-naphthyl)-5-((4-piperidinyl)methylamino)-1H-pyrazole in 40% yield. ES-MS: $(M+H)^+$ 339.

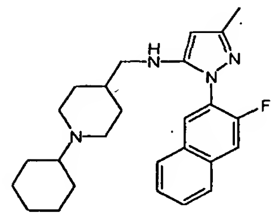
Step 3. The above amine (50 mg, 0.15 mmol) was dissolved in 4 mL methanol. To it were added acetic acid (0.2 mL), acetone (0.22 mL, 3 mmol), $NaBH_3CN$ (38 mg, 0.6 mmol). The mixture was stirred at 50 C for 6 hrs. The title compound was isolated with prep HPLC in 55% yield. ES-MS: $(M+H)^+$ 381.

<u>Example 329.</u>



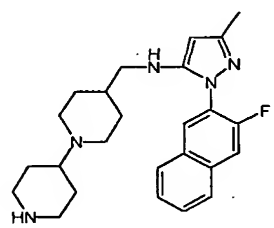
The title compound was prepared using the same methodology described for Example 328, with cyclopentanone substituted for acetone. ES-MS: $(M+H)^+$ 407.

Example 330.



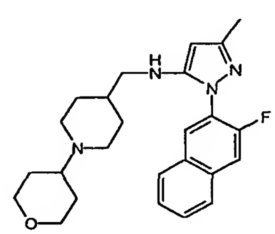
The title compound was prepared using the same methodology described for Example 328, with cyclohexanone substituted for acetone. ES-MS: $(M+H)^+$ 421.

Example 331.



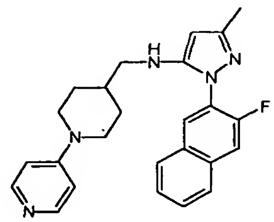
The title compound was prepared using the same methodology described for Example 328, with 4-piperidone monohydrate hydrochloride substituted for acetone. ES-MS: $(M+H)^+$ 422.

Example 332.



The title compound was prepared using the same methodology described for Example 328, with tetrahydro-4H-pyran-4-one substituted for acetone. ES-MS: $(M+H)^+$ 423.

Example 333.

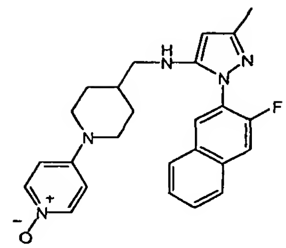


Step 1. The mixture of 4-pyridineboronic acid (0.97 g, 7.8 mmol), 4-piperidinemethanol (1.82 g, 15.8 mmol), $Cu(OAc)_2$ (2.88 g, 15.8 mmol), DMAP (catalytic amount), pyridine (2.5 mL, 32 mmol), 4A activated molecular sieve in 50 mL dry DCM was stirred for over 2 days. It was diluted with DCM, filtered through celite. It was washed with brine and water, dried, filtered through a silica plug, evaporated in vacuuo to give 4-(4-hydroxylmethylpiperidin-1-yl)pyridine in 70% yield. ES-MS: $(M+H)^+$ 193.

Step 2. The above alcohol (100 mg, 0.5 mmol) was dissolved in 4 mL dry DCM. At 0°C to it were added Et_3N (0.28 mL, 2.0 mmol) and the methanesulfonyl chloride (0.08 mL, 1.0 mmol, dropwise). After stirring for 1 hr, the mixture was stirred for another 2 hrs at room temperature. The mixture was evaporated in vacuuo to afford the crude mesylate.

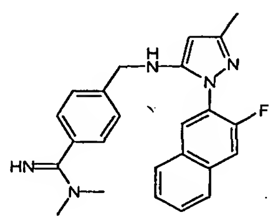
Step 3. The above mesylate was dissolved in 3 mL DMF. To it were added 3-methyl-1-(3-fluoro-2-naphthyl)-5-amino-1H-pyrazole (160 mg, 0.47 mmol) and Cs_2CO_3 (300 mg, 0.92 mmol). The mixture was stirred for overnight at 50°C. The title compound was isolated using HPLC. ES-MS: $(M+H)^+$ 416.

Example 334.



The title compound of Example 333 (12 mg, 0.03 mmol) was dissolved in 3 mL acetone. To it was added MCPBA (11 mg, 0.04 mmol). The mixture was stirred for 5 hrs. The title compound was isolated using HPLC. ES-MS: $(M+H)^+$ 433.

Example 335.

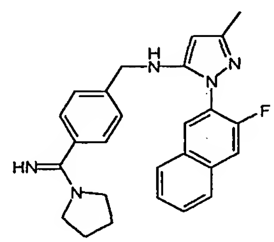


Step 1. To the mixture of 3-methyl-1-(3-fluoro-2-naphthyl)-5-amino-1H-pyrazole (200 mg, 0.48 mmol) and 4-bromomethylbenzonitrile (140 mg, 0.72 mmol) in 5 mL DMF was added Cs_2CO_3 (234 mg, 0.72 mmol). The mixture was stirred for overnight at 50°C. It was diluted with 200 mL EtOAc, washed with water X2, dried, evaporated in vacuuo, purified using flash column to afford 3-methyl-1-(3-fluoro-2-naphthyl)-5-((4-cyanophenyl)methylamino)-1H-pyrazole. ES-MS: $(M+H)^+$ 357.

Step 2. The above-prepared nitrile (30 mg, 0.08 mmol) was dissolved in 10 mL dry methanol. It was chilled and stirred in an ice bath. To this solution was bubbled dry HCl gas via a long needle till saturation reached (indicated by a blown-up balloon attached on the top of the reaction flask). The resulting solution was stirred overnight. ES-MS: $(M+H)^+$ 389. The solvent was removed in vacuuo. The residue was pumped to dryness. The solid was dissolved in 5 mL dry methanol. To it was added

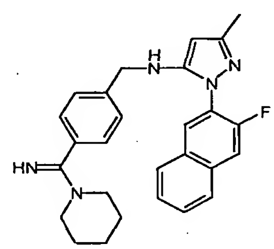
dimethylamine (2M in THF, 0.5 mL). The mixture was refluxed for 1 hour, concentrated and loaded on prep HPLC to afford the title compound in 60% yield. ES-MS: $(M+H)^+$ 402.

Example 336.



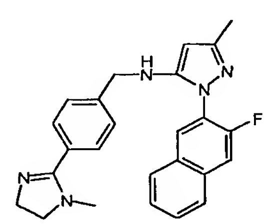
The title compound was prepared using the same methodology described for Example 335, with pyrrolidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 428.

Example 337



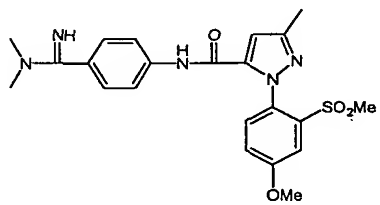
The title compound was prepared using the same methodology described for Example 335, with piperidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 442.

Example 338



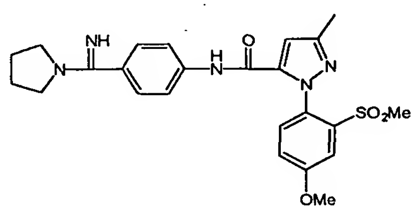
The title compound was prepared using the same methodology described for Example 335, with N-methylethylenediamine substituted for dimethylamine. ES-MS: $(M+H)^+$ 414.

Example 339



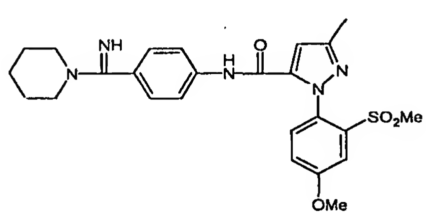
The title compound was prepared using the same methodology described for Example 231, with 2-fluoro-4-methoxyaniline substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 456.

Example 340



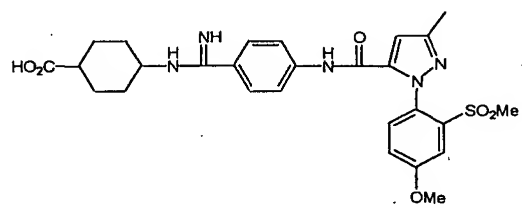
The title compound was prepared using the same methodology described for Example 339, with pyrrolidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 482.

Example 341



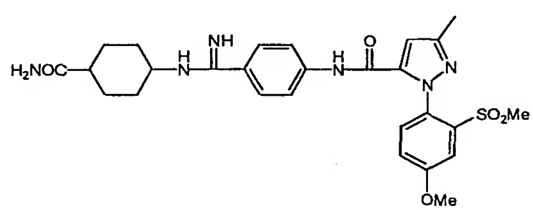
The title compound was prepared using the same methodology described for Example 339, with piperidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 496.

Example 342



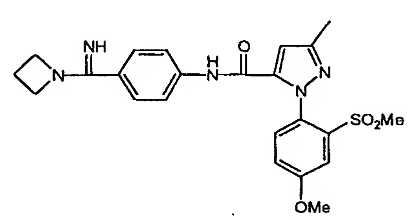
The title compound was prepared using the same methodology described for Example 339, with isonipecotic acid substituted for dimethylamine. ES-MS: $(M+H)^+$ 540.

Example 343



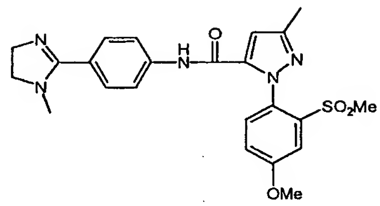
The title compound was prepared using the same methodology described for Example 339, with isonipecotamide substituted for dimethylamine. ES-MS: $(M+H)^+$ 539.

Example 344



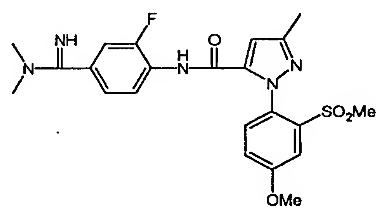
The title compound was prepared using the same methodology described for Example 339, with azetidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 468.

Example 345



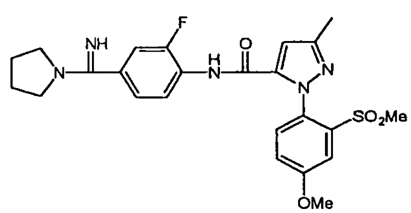
The title compound was prepared using the same methodology described for Example 339, with N-methylethylenediamine substituted for dimethylamine. ES-MS: $(M+H)^+$ 468.

Example 346



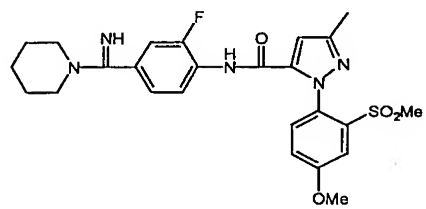
The title compound was prepared using the same methodology described for Example 339, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 474.

Example 347



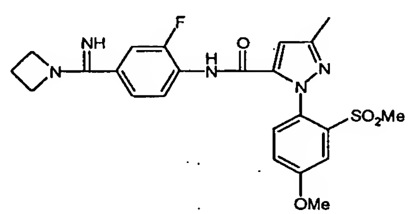
The title compound was prepared using the same methodology described for Example 340, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 500.

Example 348



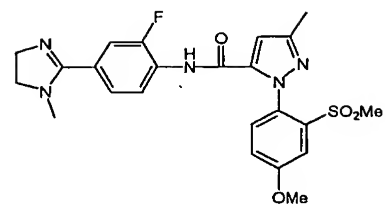
The title compound was prepared using the same methodology described for Example 341, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 514.

Example 349



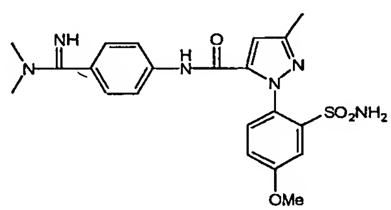
The title compound was prepared using the same methodology described for Example 344, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 486.

Example 350



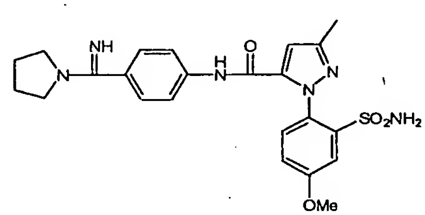
The title compound was prepared using the same methodology described for Example 345, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 486.

Example 351



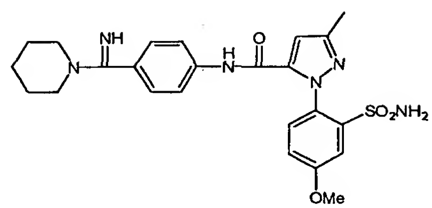
The title compound was prepared using the same methodology described for Example 240, with 2-fluoro-4-methoxyaniline substituted for 3-fluoro-2-naphthylamine. ES-MS: $(M+H)^+$ 457.

Example 352



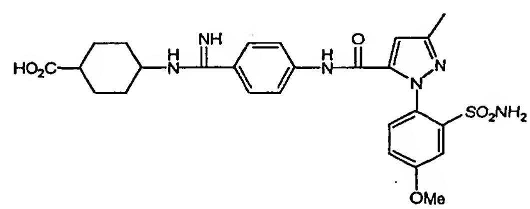
The title compound was prepared using the same methodology described for Example 351, with pyrrolidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 483.

Example 353



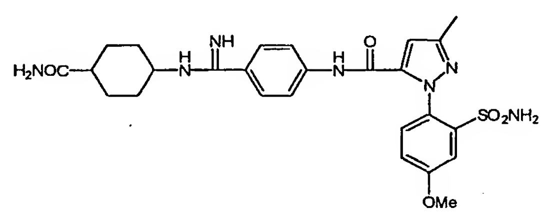
The title compound was prepared using the same methodology described for Example 351, with piperidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 497.

Example 354



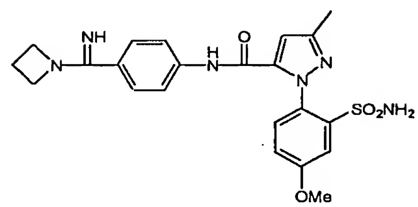
The title compound was prepared using the same methodology described for Example 351, with isonipecotic acid substituted for dimethylamine. ES-MS: $(M+H)^+$ 541.

Example 355



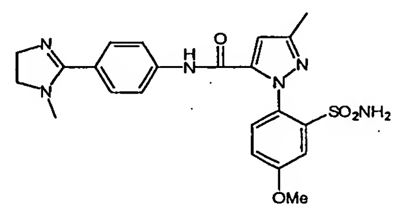
The title compound was prepared using the same methodology described for Example 351, with isonipecotamide substituted for dimethylamine. ES-MS: $(M+H)^+$ 540.

Example 356



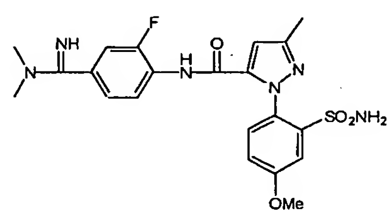
The title compound was prepared using the same methodology described for Example 351, with azetidine substituted for dimethylamine. ES-MS: $(M+H)^+$ 469.

Example 357



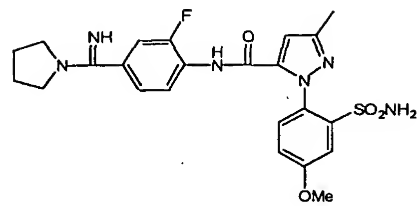
The title compound was prepared using the same methodology described for Example 351, with N-methylethylenediamine substituted for dimethylamine. ES-MS: $(M+H)^+$ 469.

Example 358



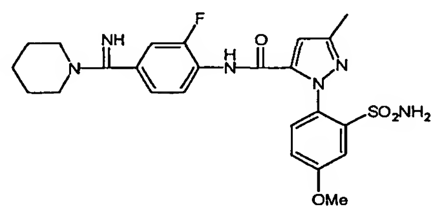
The title compound was prepared using the same methodology described for Example 351, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 475.

Example 359



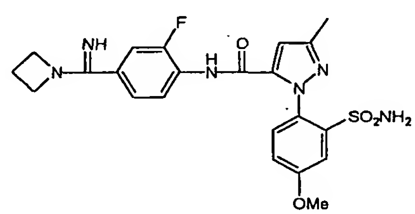
The title compound was prepared using the same methodology described for Example 352, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 501.

Example 360



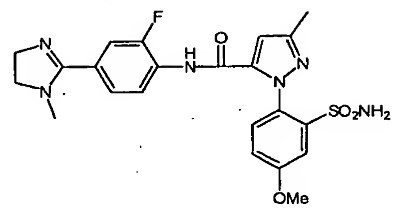
The title compound was prepared using the same methodology described for Example 353, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 515.

Example 361



The title compound was prepared using the same methodology described for Example 356, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 487.

Example 362



The title compound was prepared using the same methodology described for Example 357, with 4-amino-3-fluorobenzonitrile substituted for 4-aminobenzotrile. ES-MS: $(M+H)^+$ 487.

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of this invention is guided by in vitro protease activity assays (see below) and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μM. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC_{50} of a compound is determined from the substrate turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC_{50} of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC_{50} of less than 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC_{50} of greater than 1.0 μM in the thrombin assay, preferably greater than 10.0 μM, and more preferred compounds have an IC_{50} of greater than 100.0 μM in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and were determined using

the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma free system with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μM) in 20 mM Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM $CaCl_2$ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Eight different concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex are used for determination of percent inhibition.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. et al., Thromb. Haemost. 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and

during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

Effects of Compounds in Rabbit Venous Thrombosis model

Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at the higher doses evaluated. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 μg/kg + 2.57 μg/kg/min). Compounds have no significant effects on hematological parameters as compared to saline controls. All measurements are an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean $\pm$ SD.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.